The new genomics: challenges for ethics

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The new genomics

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The research of the study presented in this thesis was carried out in a number places. Part of the research was performed at the EMGO Institute of the VU university medical center, Amsterdam, the Netherlands, where I enjoyed the hospitality of the Section Community Genetics, in collaboration with the Department of Clinical Genetics. Substantial research was carried out as part of the Personal Genome Project in cooperation with the Genetics Department and the Lipper Center for Computational Genetics, Harvard Medical School, Boston, MA, USA. The final part of the work on this thesis was performed at the Department of Molecular Cell Physiology, Faculty of Earth and Life Sciences of the VU University, Amsterdam.
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Front cover: (1) gene fragments moving in lanes through a gel. In this case, denaturing gradient gel electrophoresis (DGGE). Photo provided by Wilfred Röling, VU. (2) Gene expression data matrix (fragment). Nature, 415:532 (2002)
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The new genomics: challenges for ethics

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
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De Boelelaan 1105

door

Jeantine Elizabeth Lunshof

geboren te ’s-Gravenhage

promotoren:	prof.dr. M.C. Cornel
	prof. R. Chadwick
copromotoren:	prof.dr. T. Pieters
	dr. C.G. van El

To my parents, who left too early
To my soulmate, always around

"I am one of those who believe that science is a thing of great beauty".[1]
Marie Curie

Preface

The thesis that is before you comprises articles written in the past few years since 2005. But the research it is based on reaches back as far as 1988. I would like to use this Preface to briefly outline the history and the background of my research and also take the opportunity to extend my gratitude to some of my past and current teachers, apart from the Acknowledgements (see chapter 11) to those who have been involved with the actual thesis recently.

In 1988, as an ethics consultant to the VSOP (the Dutch Genetic Alliance)[2], I first became involved with human genetics and with the impact of human genetic variation on the lives of individuals and families affected by specific genetic disorders. The focus of the advisory work for this association of genetic interest groups was on the social and societal context of genetics, notably the availability of and access to genetic information and services, the place of genetic disorders on the health policy agenda, regulatory issues and the relevant normative frameworks. While genetic disorders are the same, as is genetic science, the social perception of people affected by genetic disorders and the options open to them differ considerably depending on where people happen to live, it even differs between countries as close as Germany and the Netherlands. Today, I would describe this as an instance of "Global genomics – local ethics" (see Chapter 8.3.1).

In 1989, Professor Dr. Harry M. Kuitert of VU University Amsterdam, Chair of Ethics, Department of Theology, encouraged me to make these differences in 'genetic choices' the topic of a PhD project with a particular focus on comparative ethics. However, by the time a comprehensive research proposal[3] was ready for submission, the Dutch funding agency had decided to give up completely the section of its grant program for which the proposal had been intended. Research into the societal aspects of genetics was deemed premature and not to be prioritized.

Several years later a 3-year project was funded in Germany, an empirical study comparing the views of representatives of patient organizations (concerned with genetic disorders) and clinical geneticists concerning the acceptability of genetic diagnostic testing and its anticipated social consequences.[4] The study was performed at the Institute for Human Genetics, Department of Cytogenetics, University of Heidelberg (Germany), under the supervision of Professor Dr. Traute M. Schroeder-Kurth. Many years later I had the opportunity to cooperate with Professor Dieter Birnbacher, University of Düsseldorf, and carry out a critical analysis of moral arguments, as used in reproductive decisionmaking that sharpened my mind.

Even if this thesis does not include any material from these previous projects, it can be seen as a step in a continuous development that started in 1988.

However, some thoughts reach still further back. The reference made to the Buddhist axiology in the section on Global genomics – local ethics is based on my early studies of Tibetan Language & Culture at the University of Hamburg. The Buddhist value system provides a good example to illustrate the plurality of basic concepts in morality that I try to capture in 'local ethics'. At the same time it does honor to my teachers, the late Rinpoche Kenday Lotyo and Professor Dr. Lambert Schmithausen. I was more than happy to find the current lecturer at the Hamburg institute, Dr. Dorji Wangchuck, willing to give advice on the relevant part of my text and his explications and my learning bridged a time gap of thirty-four years.

My teachers from more recent years and from a different culture, Professor Michael Weingarten, Dr. Terry Bard, Dr. David Gurwitz and Ruben van Coevorden may wonder why I did not refer to the values of Judaism and to Jewish medical ethics, from Maimonides to Jakobovits and to the very broad spectrum of contemporary Jewish thought. The main reason is that we tend to recognize 'local ethics' in particular in the encounter with 'moral strangers'[5] and Jewish philosophy is too much a foundation stone of current mainstream biomedical ethics to be morally 'strange', at least at first glance in the very concise and inevitably superficial context of this thesis.

Genetics, genomics has gained momentum in an unprecedented way over the past few years and the work on this thesis was marked by it. My intuitions about the truth of the assertion of Professors Ruth Chadwick and Bartha M. Knoppers that "Ethical thinking will inevitably continue to evolve as the science does …"[6] proved to be right. Moreover, it is not just genomics as such – or the other emerging ~omics – that is evolving: the way in which we acquire knowledge develops at least as fast. We gather data without waiting for the guiding question. With relevance to ethics this means that including human subjects in hypothesis-free research implies seeking consent for unknown and unpredictable goals. At the same time, the new availability and accessibility of both science information and personal data change research subjects into active participants and self-determining agents. That seems to undermine all established frameworks of ethics. Discussions with research policy makers in the US, in the Netherlands and in Germany show that – at the time of this writing, in Summer 2008 – the problem has been spotted and that, as a consequence, many feel at a loss. With this thesis I like to put arguments forward to rather see this development as a challenge than as an imminent doom.

Since 2006, I had the privilege of looking over the shoulders of the colleagues in the lab, at the frontiers of science. It made my thinking evolve. I am in particular indebted to Professor George Church for sharing his ongoing curiosity and teaching me ever more of the spirit of adventure.

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Contents

1.

Introduction

1. Introduction

1.1 Introduction

Are new concepts needed in biomedical ethics to keep pace with the developments in post-Human Genome Project genomics?
What concepts and what ethics are meant? This thesis focuses on the challenges that developments in post-Human Genome Project (HGP) genomics pose to the established concepts and practices of – Western world – procedural normative ethics, as applied to the biomedical sciences.
These challenges are relevant to the various roles that ethics plays, as for example, its role in the design and the conduct of studies, its role in the translation of knowledge and technologies beyond the research stage, and its functioning as an instrument in the toolbox of governance.
In short, the question here is not about the ways in which ethics influences genomics, as for example by putting constraints on certain applications, but rather the other way round: how does genomics impact on ethics, in particular by shaping its role as a utility. Moreover, it will be shown that this role became self-fulfilling until it now seems to have reached its limits.

1.2 In need of a new bioethics ?

"Do we want to develop bioethics as an abstract pursuit, describing and exploring the moral constructions that society is building around genomics, or do we want to provide pragmatic, moral guidance to all that are affected by genomics?"
This outcry in an anonymous Editorial in Nature Genetics[1] calls for reflecting upon the expectations among scientists concerning the role of ethics.
And, the somewhat disappointed conclusion that: "The work of traditional ethicists is most likely to be published in ethics journals (where ethicists talk to ethicists)", entails an appeal to do otherwise. With this in mind, the papers in this collection have been written for and published in journals that address a readership with a background predominantly in the natural sciences.
Moreover, the call in this Editorial indicates a genuine interest in issues that are – rightly or wrongly – perceived of as related to ethics. Which immediately raises the question: why? How could it happen that ethics, usually in ELSI wrapping, gained such importance in genomics?

Tentative answers to this question are being provided by various disciplines, in particular from the field of the social sciences, including the political sciences, but here the question will be examined from the viewpoint of the discipline of ethics itself. Though sometimes it seems as if 'ethics' has become an object of social sciences research only recently[2], the discipline by tradition reflects upon itself in its branch of meta-ethics.

Governance

One important subject in social science research is 'governance', and the relation between governance, ethics, and genomics has received a great deal of attention in the recent literature.[3,4,5] The history of ELSI in genomics reveals the intricate nature of this relationship: it shows the institutionalization of ethics as an instrument for the governance of genomics.[6] Used as a multifunctional instrument ethics offers, among other utensils, both procedural and conceptual tools – in this function it is like the Swiss knife of governance. Ethics is called upon to provide the legitimization for the procedures of governance, notably by putting forward the structures that enable the – perceived – ethically correct oversight and regulation. At the same time, ethics provides the moral concepts that are the source of the values used to actually legitimize the goals of a particular governance framework. Frequently, by invoking 'high' concepts like human dignity that subsequently are used as crowbars for the justification of policies.[7,8,9] This way, the role is shaped of applied normative ethics as 'serving the moral constructions that a society is building'.[1] In the field of genetics and genomics this application of ethics has been regarded as very adequate for obtaining moral guidance for several decades, but now it apparently does not meet the expectations any more. Moreover, from the point of view of the discipline itself, the instrumental use of ethics may be detrimental to philosophical rigour.[10,11]

1.2.1 Fundamental questions

This image of ethics, as a multipurpose instrument raises several fundamental questions:

- is this assigned role, in particular as a governance tool in accordance with the genuine business of ethics in the form of applied normative ethics, including bioethics?
- what specific features of (bio)ethics made its practice be so strongly determined by the demands from governance and the societal expectations? The application of ethics to issues related to genetics and genomics may serve as an exemplar.
- what is the challenge for ethics as such in this context? What does it mean for its 'practice' and for its integrity as a philosophical discipline?[11,12]

The decision to investigate the emerging issues in a way that is relevant to scientists from the biomedical and life sciences, and to participate in the discussion in the journals that are addressing this readership, has shaped the approach taken in this study.

1.3 Aim

The aim of this study is to analyze the role of ethics in genomics and the related sciences and to generate hypotheses concerning future developments in ethics, taking into account the likely paradigm shift in the genomic sciences towards systems biology.

1.4. Method

From the outset, this project has followed a hypothesis generating approach rather than focusing on a narrow research question. Initial observations from the literature in pharmacogenetics (PGt) and pharmacogenomics (PGx) showed a discrepancy between the role this field attributes to ethics, and the professional understanding of that role by the discipline of ethics itself.
One resulting hypothesis was, that including paragraphs on 'ethics' in scientific articles most likely is a response to governance demands: paying lip service to the call for adhering to moral principles (in the awareness that 'ethical correctness' is a prerequisite for obtaining funding), and/or bridging the gap to implementation by offering a handle for governance (in the awareness that PGx must be translated into clinical practice in order to establish clinical validity and utility). This observation generated further questions concerning the relation between ethics and governance and broadened the investigation to cover the wider field of genomics.
Hypothesis-generating – or even hypothesis-free – research is increasingly important in the sciences, and in genomics and systems biology in particular. Much of post-genomics research is data-driven, in terms of Westerhoff and Kell: "a good hypothesis being the result, not the starting point of the investigation".[12] Though, as these authors and others stress, hypothesis-generating (inductive: from data to ideas, according to Kell and Oliver)[13] and hypothesis-driven (deductive: from ideas to data) are not competitive but complementary, working in iterative interplay.

In the humanities, hypothesis-generating research, starting without a clearly delineated research question and aiming at no more than a hypothesis to be the outcome, is not a regular research model.[14] Its deliberate application can be seen as an innovative approach, in this case necessitated by the dynamics of the developments in the field of post-HGP genomics in which the empirical facts change faster than any hypothesis as a starting point can take into account. Therefore, as the impact of these dynamics became clear from the initial observations of developments in PGx, a flexible strategy was chosen which included zooming in on two concrete cases: the Personal Genome Project (PGP)[15], and the Pharmacogenetics Research Network (PGRN) with its Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB).[16]

In both cases ethical expertise was called upon in questions concerning, among other things, data collection, data sharing and informed consent. The issues at stake, notably privacy, confidentiality, voluntariness and consent, are traditional cornerstones of research ethics. The issues are highly relevant to governance because of their role in justifying and determining the establishment of regulatory frameworks and, besides, they contain the whole package of moral values.
In both cases, in view of the developments in science and technology and the rapidly changing empirical facts, a clear need was felt for reassessment of procedural aspects and reflection upon the underlying moral concepts. This led in both cases to substantive professional involvement with the concrete development of informed consent protocols.

It should be stressed, that the publications that make up this study are not reports of systematically conducted participatory observation, but result from committed professional involvement in multidisciplinary research teams.

1.5 Ethics, genomics, governance

Ethics, genomics and governance have been developing separately, but in a parallel way, each at its own pace, running in lanes like DNA or RNA molecules in a gel (see front cover). In the following I will give a short introduction into these developments, aiming at just providing a basic understanding of the context of the questions that are central to this study.
First, I will describe the emergence of a rights-based ethics that was particularly suitable for becoming an instrument of governance (in contrast with any type of virtue ethics that is of little use for modern Western world concepts of public policy and governance), and parallel the development of genetics, via the molecular 'new' genetics to genomics. The rise of the new genomics and post-genomics implied an increasing globalization, requiring appropriate governance structures – which in turn required the institutionalization of a predominantly procedural ethics, thus rounding the circle and reinforcing ethics in this particular role. Second, there will be a short section on the relationship between ethics and governance, showing again how institutionalization of ethics implies its use as a governance instrument.
The history of ELSI, ELSA and the establishment of ethics within HUGO provides a nice illustration of the above.

The relevant notions of genetics, new genetics, genomics, new genomics, post-genomics and systems biology will be described in keywords in a separate section (1.5.3).

1.5.1 Ethics & genomics

In a way, one could say that ethics has moved from the bedside to the bench and from there to the biobank – from which it will hopefully return to the bedside[17] – a journey that I will briefly describe below. More thoroughly, one can say that two particular strands of normative ethics have extended their field of application following the development of medicine and biomedical research. These two strands are clinical medical ethics and biomedical research ethics. Both strands are intimately connected and have much content in common, each having a procedural and a conceptual side. The current picture of post-genomics research ethics shows the outcomes of a shifting emphasis between the procedural and conceptual component of both strands, resulting in a largely procedural normative framework. Though, as a firmly established procedural framework it would be considered to be particularly robust, it seems to have reached its limits now. A number of factors have contributed to that: the empirical basis has changed, and developments in science and technology, such as in genotyping technologies, have made obsolete (part of) the factual assumptions that the framework was built on. New research strategies and changes in theoretical understanding up to a paradigm shift are changing the

known pathways of research to which normative frameworks refer. Globalization, on the other hand, and an increasingly important role of strong partners from non-western cultures call the sustainability of established normative concepts (developed by Western cultures) into question. And lastly, the changing position of the individual, influenced by increasing direct access to actionable knowledge makes it necessary to take new models into account: a remodeling of 'patients' or 'research subjects' into *individuals as agents* (confident citizens, consumers of personal genomic information as a commodity) is around the corner. This latter shift may in fact have the profoundest influence on post-genomic ethics.

1.5.1.1 From the bedside to the bench to the biobank and back

Medical ethics, by tradition, is concerned with moral issues in the patient-physician relationship like confidentiality, consent, and the avoidance of harm, the latter also expressed in a paternalist way through setting limits to information and truth-telling.

Research ethics with a strong focus on biomedicine developed in the second half of the 20th century, initially as a reaction to atrocious experimentation with humans by physicians during the Nazi regime.[18] Later, the need for regulation and control was reinforced elsewhere, as serious abuse of human subjects in medical research in the post-war USA became public.[19] These origins led to the protection-paradigm become the hallmark of research ethics.

From this point on there were two strands: the classical strand of clinical medical ethics with emphasis on moral content – in part in the form of virtue ethics –[20], and the new strand of research ethics with a strong emphasis on normative regulatory frameworks.[21] At the same time regulatory aspects entered clinical medical ethics under the influence of the developing field of health law with the emerging concepts of patients' rights (incorporating moral and legal aspects) being a major novelty.[22] In research ethics, for its part, the regulatory frameworks were justified by reference to the traditional values and the modern individual rights from clinical medicine.[23] In this sense there were again two strands, with frequent crossing over. Clinical medical ethics remained to some extent local, due to considerable variation in medical culture, professional rules, and national legislation, and perhaps one should add: local virtues. Research ethics rapidly became international and global with research – mostly pharmaceutical – crossing borders and with international organizations taking up leadership in the development of regulation.[24] At this point, the transition of normative power towards governance took place with ethics becoming one of its instruments. In parallel, 'principles of biomedical ethics' were established and codified in a textbook by Beauchamp and Childress that has remained, with regular revision, a cornerstone of bioethics.[25] The approach taken by Beauchamp and Childress addresses ethical issues arising in the clinical and in the research context. For the latter it turned out to be particularly useful, as this approach offers clear structures for the analysis of the broad range of issues that must be dealt with in the context of human subject research. I would contend, that the successful application of the principle-based approach to research has played a crucial part in establishing the predominance of the procedural side of (bio)ethics in general, thereby – as a side-effect – optimizing and underscoring its usefulness as a governance tool.

However, this was clearly not the agenda of the original authors and neither was 'reaching consensus' a principal aim.
In clinical medicine and in clinical research the principle-based ethics model became the standard tool for guiding the assessment of study protocols by institutional review boards and other ethics committees and in many places it became reflected in health legislation. While still regarded as 'mainstream biomedical ethics', discussions about its interpretation, merits and utility are ongoing among ethicists.[26]
At the larger scale of research governance, as e.g. in the Human Genome Project, the Beauchamp & Childress principles were applied early on as a matrix for the design of the ELSI component of the program and the internal project regulation. In particular, the principles were used as a way to reach – international – consensus on controversial aspects of the HGP.[27] In a review ten years later, Knoppers and Chadwick note a shift in the applicable principles and suggest a revision.[28] However, as indicated above, the entire scenery has changed and new realities must be taken into account for post-genomics research ethics to meet the new demands that pertain to the procedural as well as the conceptual part of biomedical ethics.

1.5.2 Ethics & governance

As mentioned above, the relation between governance and ethics has received a great deal of attention recently. Governance is a notion that is in particular at home in the social sciences and political philosophy. Examples of definitions are: "*Governance* can be seen as the totality of theoretical conceptions on governing"[29] and "Governance is a social function centered on the making of collective choices regarding matters of common concern to members of human groups".[30] In an introductory text on genetics and governance Bunton and Petersen invoke Foucault and concepts of 'bio-politics' and 'governmentality' to sustain their claim for an integration of ethics and governance before proceeding to an analysis of the relevance of governance for genetics.[31]
Their argument nicely illustrates the intricacies of the relationship between ethics and governance – and of the representatives from both realms – as it amounts to the deliberate reduction of 'ethics' to just one single utensil of the Swiss knife: ethics as a procedural tool, presupposing that the knife essentially is an instrument of governance.
It is true that: " 'Ethical' issues are seen as clearly delineable and governable through mechanisms such as protocols, ethics and governance frameworks, and ethics committees".[32] But this is the dream of governance rather than a description of the genuine business of ethics. However, as I have argued above, when ethics becomes 'institutionalized' it almost inevitably becomes converted into an instrument of governance. The perfect real-life example of this process of institutionalization can be observed in the establishment and prospering of ELSI and ELSA that were purposefully created to be instruments of governance. Yet, this does not turn governance into ethics or vice versa.

ELSI / ELSA - definitions & origins		
Acronym	**ELSI**	**ELSA**
Full	Ethical, Legal, and Social Issues	Ethical, Legal and Social Aspects
Initiated by	U.S. Department of Energy & U.S. National Institutes of Health	European Commission
Context	U.S. Human Genome Project (1986)	The Second Framework Programme (1987-1991): pilot programme on human genome analysis, focus: 'predictive medicine'
Preparatory work	1988	1988
Purpose	Studying the ethical, legal, and social issues surrounding the availability of genetic information	[promoting] research on the societal issues concerning regulation and desirability of the life sciences and technologies
Established	1990	1994 European Commission, Ethical, Legal and Social Aspects of the Life Sciences and Technologies of the Fourth RTD framework Programme (1994-1998)
URL	http://www.genome.gov/10001754	http://cordis.europa.eu/elsa-fp4/src/publics.htm

Table 1

1.5.2.1 Institutionalization: ELSI, ELSA & HUGO

A brief description of the development of ELSI, ELSA, and of the integration of ethics in HUGO, will show how ethics ended up in the toolbox of governance instruments.

ELSI

The phenomenon of 'ELSI' – today a common and popular acronym – is a creation of the U.S. Human Genome Project (HGP). The formal definition of ELSI and a description of its function and purposes can be found in the first report of the Working Group on Ethics of the Program Advisory Committee on the Human Genome. Preliminary work had been done since 1988. According to this report, that is summarized in the 1990 DOE-NIH report Understanding Our Genetic Inheritance[33], the ELSI program should address the implications for individuals and society of the mapping and sequencing of the human genome. This included examining the ethical, legal, and social consequences, stimulating public discussion and developing policy options to assure a beneficial use, for individuals and society, of the anticipated HGP information. Fairness in the use of genetic information, the impact of knowledge of genetic variation on individuals, and privacy and confidentiality of genetic information are among the focus areas.

From the beginning, there has been a strong focus on the consequences of the medical applications resulting from the genome program: predictive genetic testing, the gap between diagnostic and therapeutic possibilities, and concerns about privacy and confidentiality beyond the patient-physician relationship.

However, as the report from 1990 states "These questions are not new. Physicians and counselors are facing them today when treating patients with genetic and other diseases".[34] Relevant examples are earlier policy documents, notably the 1988 report on genome projects[35] and the 1983 report on genetic screening[36] that contain substantial chapters on 'social and ethical considerations', and 'ethical and legal implications' respectively. The 1983 report already clearly shows the nexus between governance and ethics, parts of which still seems to fit within the current paradigm as it has developed over the subsequent 25 years.

Relevant points for the further line of argument:
• The establishment of the ELSI-program as integrated component of the Human Genome Project is the turning point that marks the institutionalization of ethics[37] in the context of science policy in genetics (later: research governance in genomics).
• ELSI is supposed to cover legal and social issues as well, but ethics gets more than its share: the HGP ELSI program later being presented as "... the world's largest *bioethics* [emphasis J.L.] program, which has become a model for ELSI programs around the world".[38]
• The aims and focus of the program, the issues that are being dealt with, and the ethical framework that is being employed, are not new.

ELSA

In Europe, as in the U.S., the ethical, legal and social aspects of genetics have been recognized as relevant issues for policy making since the rise of clinical genetics as a medical specialty. The discipline's profile was raised, as developments in molecular genetics (notably the discovery of restriction fragment length polymorphisms – RFLP's) were put into practice in clinical diagnosis. The ability to perform direct DNA diagnostics, independent of the availability of the gene product was a revolution worthy of the term "New Genetics".[39] It opened up a new dimension in particular in prenatal diagnosis. In the Netherlands, the Health Council published in 1980 a report on the ethics of genetic counseling[40] that already includes a number of issues that keep clinical geneticists and bioethicists busy till the present day. For example, professional confidentiality, information sharing within families, the counselor's role in 'responsible' decision-making, and also the potential conflict between individual and public interests. An earlier (1977) Health Council report on genetic counseling[41], did not yet involve substantial ethical, legal or social considerations. The turning point for including these aspects in policy documents thus seems to be around 1980, also in the international context.

European ELSA has a story very similar to that of her American sister ELSI.[42] Preliminary activities took place in 1988. The Second Framework Programme of the European Commission (1987-1991) was to include a pilot program on human genome analysis with focus on 'predictive medicine'. As this met with opposition, the European Parliament required an ad hoc ethics committee to be installed on ESLA – Ethical, Social and Legal Aspects. The Third Framework Programme (1991-1994) included Medical Ethics as a sub-area to Biomedicine, and finally, in the Fourth Framework Programme (1994-1998) ELSA became an integrated part of

Life Sciences & Technologies, with a funding of 2% of the S&T budget. Of note, contrary to ELSI as tied to the U.S. genome project, the European ELSA activities have never been restricted to biomedicine or genetics but are intended to cover all areas of the life sciences. Though ELSA, like ELSI featuring 'bioethics', was officially established with the 4th F.P., projects including research into the ethical, legal, and social aspects of genetics were carried out since the 2nd F.P..

HUGO

Not by coincidence, but driven by the increasing scale of genome research – facilitated by technology development – and the upcoming strong international competition, the Human Genome Organisation was founded in 1988 at the first meeting on genome mapping and sequencing at Cold Spring Harbor. At a time that human genome initiatives were launched in various countries this organization was conceived as an international coordinating scientific body. By some of its founders it was seen as a "U.N. for the Human Genome".[43] From the start, its purposes included "to encourage public debate and provide information and advice on the scientific, ethical, social, legal, and commercial implications of human genome projects". HUGO established its Ethics Committee in 1992.[44] Both the organization as a whole and the ethics committee are intended to be bodies of governance and the mission statements explicitly refer to ethics as an instrument to regulate practices with the aim of promoting – perceived – moral and non-moral goods, i.e. "the regionally-appropriate, ethical utilization of [genomic] information for the good of the individual and the society".[45]

Genetics & Genomics[46]
Genetics is the study of single genes and their effects
Genomics is the study of the functions and interactions of all the genes in the genome and with the environment

Table 2

1.5.3 Genetics, genomics & systems biology – a glossary

Genetics and genomics language may be confusing. The terminology differs and depends upon the context and the discipline of the author. Above I referred to the use of "new genetics" in the context of the social sciences.[47] Comprehensive research has been conducted in the fields of sociology and history of science, and in science and technology studies. These in-depth analyses, however relevant, are outside the scope of this study. Also the notion 'gene' in itself has come under philosophical scrutiny recently.[48] These challenging and highly sophisticated

interpretations are valuable contributions in a critical debate about "genetics" or "genomics", but they are not very helpful for general communication. Here, no more than a glossary will be provided, only keywords/sentences highlighting especially the chronological order of the marked introduction of terminology that appears to be tightly connected with advances in technology. No other ~omics are included.

Genetics: the study of single genes and their effects. Genetics is also the study of inheritance in general. It pertains to all organisms. Human genetics has developed in the second half of the 20th century in particular as 'disease' genetics: clinical or medical genetics. As in other areas of medicine, advances in science and technology provided the clinicians with increasing knowledge and diagnostic methods concerning hereditary disorders.[49] The clinical focus included also the adoption of the normative framework of medicine, and established concepts of medical ethics were integrated in the theory and practice of clinical genetics.

New genetics: the "new genetics" is a coined term and its origins can be traced exactly: it was introduced by David Comings in an editorial in the American Journal of Human Genetics in 1980.[39] He used it to describe the new diagnostic options (that he envisioned in particular in the realm of prenatal diagnosis) through technological advances that significantly improved gene mapping, thus allowing efficient detection of – disease related – stretches of the genome. Ten years later, David Weatherall phrases it in simpler terms: the 'new genetics' stands for the study of inheritance at the molecular level.[50]

Genomics: the term was coined in the Editorial of the first issue of the journal with the same name, by McKusick and Ruddle in 1987.[51] They introduced this notion to capture research on the genome (human and of other organisms) that involves mapping, sequencing and the analysis of the information. They note, in 1987, that mapping efforts (determining the location of genes on chromosomes and their relative positions to each other) have begun 20 years earlier and sequencing (determining the sequence of the nucleotides that make up a genome) about 10-15 years ago.
In terms of the National Human Genome Research Institute (NHGRI)[52]: genomics is the study of the functions and interactions of all the genes in the genome and with the environment.

New genomics: also the origins of 'the new genomics' can be traced exactly. In a Policy Forum contribution in the special Genome Issue of Science, October 1996, Eric Lander proposes 10 goals for the next phase of genomics: after the completion of the first steps in the Human Genome Project – the genetic mapping of the human genome and fast progress with the physical mapping, now the sequencing phase had begun. The next steps, towards the 10 goals, include the transition of the results from the era of structural genomics into tools for the era of functional genomics.[53]

Post-HGP genomics: since the publication in February 2001 of the working draft of the human genome, and definitely since the official completion of the sequencing of the – composite – human reference genome in February 2003, all genome research has become post-HGP.[54] The real impact is – beyond formal terminology – in the further direction and content of research. Post-HGP genomics is directed towards functional genomics of which proteomics currently is a main branch. Further ~omics branches, as e.g. transcriptomics, metabolomics, epigenomics, microbiomics are developing. Computational biology and bioinformatics are crucial for navigating in these data-rich fields of integrative genomics. Technology development is the other prerequisite for the advancement of post-HGP genomics.

Postgenomics: postgenomics emerged long before post-HGP genomics, as a prelude to the transition towards the new biology.[55] By 'making biology computable' it bridges functional genomics and computational biology, contributing to systems biology.

Systems biology: systems biology is an integrative science. It combines existing disciplines – e.g. physics, chemistry, molecular biology, mathematics – in an integrative biology with a new focus. One definition is: "the science that discovers the principles underlying the emergence of the functional properties of living organisms from interactions between macromolecules".[56] However, there is a range of other definitions. Systems biology is a program with a complex agenda, including substantial philosophical reflection and analysis of the conceptual framework of the discipline.[57] Although the origins of systems biology can be traced to the 1950s and 1960s, the term itself has only appeared in the scientific literature in 1999[58] and has since led to the establishment of several dedicated research institutes, for example the ISB (Seattle, U.S.A.) in 2000[59] and the SBI (Tokyo, Japan) at the same year.[60]

1.6 Content – Overview of chapters

A short overview of the articles that form the following chapters of this thesis.

Chapter 1 consists of the foregoing **Introduction.**

Chapter 2 The new genomics: new challenges for ethics? The article *The new genomics and personal genome information: ethical issues* takes the ethical issues surrounding 'new style' personal genome information as an example to explore the questions that are raised by developments in next-generation sequencing technologies.

Chapter 3: Shifting trends in ethics discusses in the article *Personalized medicine: new perspectives – new ethics?* the applicability of protection-paradigm based principles to questions arising from the potential conflict between individual and collective interests in population-based genomic research.

Chapter 4: Genomics for all – ethical implications for clinical practice presents some possible consequences for the physician-patient interaction in view of the new reality of comprehensive personal genome information being available to any individual who wishes to purchase it: *Hippocrates revisited? Old ideals and new realities.*

Chapter 5: New roads to consent. In search of pragmatic moral guidance. This chapter zooms in on the first demonstration case of this study and addresses the concrete question of obtaining valid consent for participation in state-of-the-art genomics research that involves collecting and sharing of comprehensive genotype-phenotype data sets. In *From genetic privacy to open consent* it is argued that 'veracity' should be the primary moral principle guiding novel models of consent.

Chapter 6: Current challenges for consent: pharmacogenomics, data sharing, and the language of consent. Today, research uses the data from yesterday. For example in pharmacogenomics research the building of very large well-curated databases and the use of all relevant extant data is indispensable for generating reliable, validated knowledge that will be clinically applicable. In *A Call for the Creation of Personalized Medicine Databases* we argue for data sharing that includes the vast extant data bases of industry. A moral obligation may exist to use all data that individuals made available for purposes of health research.
This chapter also includes a working draft of a white paper for the NIH/NIGMS prepared on behalf of the Pharmacogenetics Research Network Data Sharing Action Group: *Pharmacogenetics, data sharing, and biobanking: the scope and limits of consent.*

Chapter 7: Outlook on theory development and education. The article *Teaching and practicing pharmacogenomics: a complex matter* discusses the importance of the application of systems biology approaches to pharmacogenomics. In particular, attention is paid to the implications of this paradigm shift for the current and future curricula in the biomedical sciences that shall enable implementation of the new approach in clinical practice.

Chapter 8 contains a **General Discussion**. This chapter recapitulates the initial questions concerning the role of ethics in genomics and, in particular, the impact upon ethics of the developments in the genomic sciences. The challenges, as posed by these developments are addressed, notably concerning scale and pace, technology and methods, theory development in

the sciences up to an evolving paradigm shift, and novel practices. Ethics also faces challenges from 'within': the global science of genomics meets local ethics – examples of 'particular moralities' are presented. Finally, the role is addressed of professional ethicists, as involved with science as 'insiders' or 'outsiders'.
An **epilogue** on **The $1000 genome** contains a reply to Nature Genetics' Question of the Year in 2007, and discusses the moral desirability of *A just distribution of benefits*.
The thesis is concluded by a **summary** in English and in Dutch.

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2.

The new genomics: new challenges for ethics?

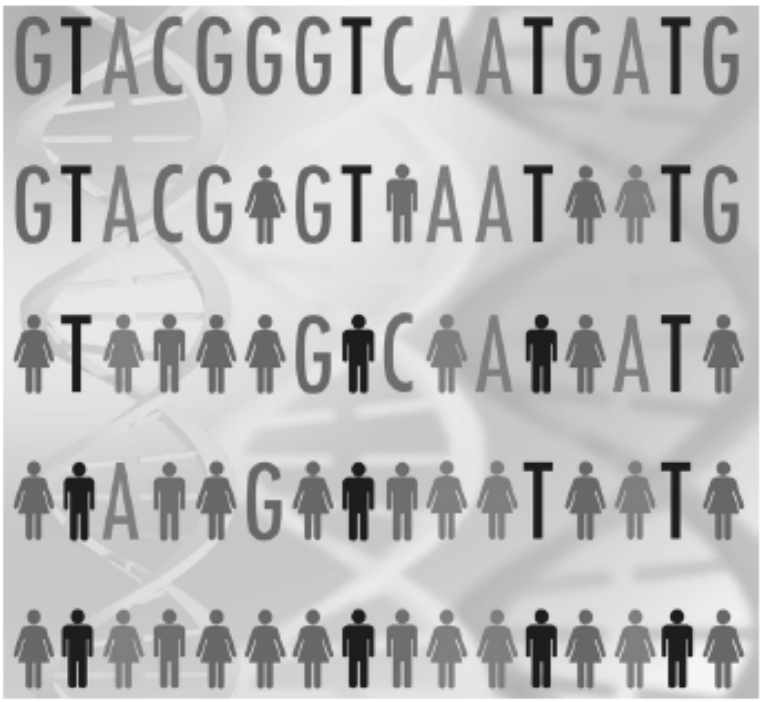
Jeantine Lunshof. The new genomics and personal genome information: ethical issues. In: M. Janitz (ed) Next Generation Genome Sequencing. Wiley-VCH, Weinheim. 2008

Edited by Michal Janitz

WILEY-VCH

Next-Generation Genome Sequencing

Towards Personalized Medicine



18
The New Genomics and Personal Genome Information: Ethical Issues

Jeantine E. Lunshof

18.1
The New Genomics and Personal Genome Information: Ethical Issues

Do developments in the new genomics, its applications, and technologies raise genuinely new ethical issues? Has biomedical ethics reached its boundaries? We must ask, whether novel concepts are needed to keep pace with the rapid developments in genomics, or whether we will be able to move the boundaries and provide answers within our current ethical framework.

The answers to these and other key questions depend on the interpretation of the role of ethics, in particular, as applied to the biomedical sciences. One possible interpretation, the one that I subscribe to, is expressed in the view that "Ethical thinking will inevitably continue to evolve as the science does . . .," as voiced by Knoppers and Chadwick [1] in their landmark study.

The need for a revision of the approach taken by biomedical ethics with regard to questions concerning genomics has been appreciated for years, but developments in ethics are slow compared to the dynamic growth of genomics research [2, 3].

In this chapter, I will first identify the features of the new genomics that pose special challenges to ethics. Then I will outline the development and the structure of the current framework of mainstream biomedical ethics. From that context, the ethical issues surrounding "new style" personal genome information will be taken as an example to explain the emerging questions and to explore possible solutions.

18.2
The New Genomics: What Makes it Special?

What is Special about the New, Post-Human Genome Project Genomics' Research? At least four striking features can be mentioned that have relevant effect on the normative and governance structures, as commonly used for dealing with genomics by society:

Next-Generation Genome Sequencing: Towards Personalized Medicine. Edited by Michal Janitz

ISBN: 978-3-527-32090-5

- *Scale and pace:* For example, the consortium efforts and networks of networks involved in genome-wide association studies (GWAS). The magnitude of the studies allows outcomes to be obtained much faster and provides the power needed for finding genome/phenome associations that would not otherwise be attainable.
- *Technology and methods:* Notably, the advances in high-throughput sequencing, but also, for example, array technology, multiplex PCR, and bioinformatics.
- *Theory development and shifting paradigms:* Hypothesis-free and hypothesis-generating research (GWAS), shift toward systems biology, and bioinformatics.
- *Novel practices:* Among other things, centralized data storage, data accessibility and sharing, and powerful web-based search engines.

A special and highly relevant feature of these developments is that we are witnessing very large-scale research, in particular the consortium efforts in genome-wide association studies, and very small-scale yet comprehensive research of individual whole genome sequencing in the form of "personal genomes" at the same time. Both applications are enabled by the new sequencing technologies and raise a specific set of ethical questions. Further advances in, for example, functional genomics, transcriptomics, epigenomics and bioinformatics, and mining of a very large number of health records will increase the information yield from the resulting comprehensive data sets, and this will also influence the potential ethical implications.

18.3 Innovation in Ethics: Why do We Need it?

The features mentioned above suggest that today's biomedical research ethics may not be fully adequate to deal with the questions that are at stake in the post-Human Genome Project (HGP) era that presently is marked by, among other things, next-generation sequencing and gene expression technologies. There is a pressing need to address questions that span from very large-scale research projects to single personal genomes. Given the dynamics of the field, we should be prepared to face more new questions and challenges soon.

To make clear the necessity of innovative solutions, we must look at the way in which biomedical ethics has developed till now. Medical ethics has come a long way since the ancient times of Hippocrates. Although this may seem very remote from the topic of new sequencing technologies and the like, we will see that the "Hippocratic ideal," as I would like to call it, influences the image of medical confidentiality until today, and this needs to be taken into account when, for example, redesigning consent for participation in studies in the new genomics.

The following section offers a short overview of the development of mainstream biomedical ethics, from doctor–patient-focused clinical ethics to research ethics, including epidemiological and other research work with groups and populations as

subjects. It will become apparent that the new genomics and personal genomes do raise some genuinely new questions that challenge the boundaries of the current normative frameworks.

18.4
A Proviso: Global Genomics and Local Ethics

One important proviso needs to be made. Contemporary Western world biomedical ethics is taken here as the reference. This should not be interpreted as a lack of awareness of the existence of important traditions of medical ethics in many parts of the world. Actually, the issue of how the ethical and legal norms that make up local normative frameworks can be incorporated into the governance of research and application of globalized genomics is a major research topic in the social and political sciences [4].

Mainstream Western world biomedical ethics is deliberately chosen here as a starting point because of its dominant role in framing regulation and guidelines for research worldwide, as well as the predominance of Western culture, values, and resources in funding and carrying out the majority of current human clinical genetics research. When we raise the question about boundaries, we mean the boundaries of this particular framework.

18.5
Medical Ethics and Hippocratic Confidentiality

Medical ethics has developed over millennia in many different cultural, medical, and religious contexts. Traditional codices may contain rules about how to behave among colleagues – medical etiquette – and how to act as a good doctor in the physician–patient relationship – medical ethics. In the Western tradition from Hippocrates to Percival and the first Code of Ethics of the American Medical Association, emphasis has been on professional virtues and, over the centuries, *beneficence* has been the core moral concept [5]. Over the centuries, the duties of the physician are fixed and made known to society in the condensed form of the physician's pledge, prayer, or oath, as from Maimonides or Hippocrates, which are being continued through the modern codices [6]. Of particular relevance to our topic of personal genome information is the universal traditional promise of *strict confidentiality* in the patient–physician relationship. The Oath of Hippocrates entails the paradigmatic commitment to professional secrecy that has been generally acknowledged as a key feature of the practice of medicine ever since.

It is very important to note that this "Hippocratic ideal" of confidentiality and secrecy is commonly present in peoples' minds today, even if the evidence suggests otherwise [7]. One illustration of the purposeful use of this omnipresent association is the fact that IBM chose the name "Hippocratic Database" for its innovative

database technology that is claimed to enable secure handling of electronic health records [8].

18.6 Principles of Biomedical Ethics

When considering modern medical ethics, we should never forget that our current twentieth-century framework of biomedical ethics arose as a reaction to a dark past of crimes against humanity, of scandals, and of medical malpractice [9, 10]. Therefore, it is no surprise that *protection* is the key concept, and the leading paradigm of biomedical ethics is the *protection paradigm*. The prime object of protection is *human dignity* [11]. Among the values derived from this core notion are the value of life and bodily integrity of individuals, the individual free will, and the acknowledgment of the right to self-determination [12, 13]. Therefore, *autonomy* is the central concept. The requirement of *respect for autonomy* has become the leading principle in postwar Western world ethics [14].

The classical principles of biomedical ethics consist of the well-known four clusters of norms that were first presented by Beauchamp and Childress in their seminal textbook, *Principles of Biomedical Ethics*, in 1979 [15]:

1. *Respect for autonomy:* Respecting the decision-making capacities of autonomous persons, this establishes the requirements of voluntariness and of consent.
2. *Nonmaleficence:* Avoiding the causation of harm.
3. *Beneficence:* Norms for providing benefits and balancing benefits against risks and costs.
4. *Justice:* Norms for distributing benefits, risks, and costs fairly.

These principles are guiding the relationship between the individual patient and the physician in clinical practice, as well as the relationships in clinical research.

18.7 Clinical Research and Informed Consent

In the context of clinical research, this model underpins the fundamental requirements of informed consent, voluntary participation free of undue constraints, a favorable risk–benefit ratio for participants, and the right to withdraw at any time from a study without consequences for medical care, to mention the most prominent ones [11]. Ethical review of whether these requirements are met and Institutional Review Board (IRB) approval of study protocols are the central procedural elements in any type of research. To protect the research subjects from harm that results from research participation is the first and foremost aim of the whole procedure. However, even the most meticulous ethics review cannot prevent

serious or even fatal harm from occurring, as recent clinical research tragedies have shown [16].

18.8
Large-Scale Research Ethics: New Concepts

Knoppers and Chadwick have presented arguments for the need of a shift in emphasis of the principles that make up the normative framework of research ethics, with focus on research in human genetics in particular [1]. Such a shift in emphasis of ethical principles does not imply disqualifying or discarding the old ones, nor does it mean giving up core moral values. As the authors say, "There might not, and cannot, be universal norms in bioethics, as emerging ethical norms are as 'epigenetic' as the science they circumscribe" [1]. Indeed, the issue of the universality of norms touches upon the most fundamental questions of ethics that will always be hotly contested and cannot be, once and for all, resolved by rational discourse [17].

The completion of the HGP has confronted us with a shift in emphasis in genomics research that can be characterized as a shift from individual and family disease-oriented clinical genetics – dominant in the early and mid-1990s – to population-directed research genetics, carried out in projects of formerly unknown dimensions and including populations and researchers on a global scale. What can be criteria to assess the ethical quality of studies targeting groups, communities, or populations? A novel set of ethical principles, very distinct from the well-known four principles and relevant to the rights and interests of groups, has been proposed. In keywords,

- reciprocity
- mutuality
- solidarity
- citizenry
- universality.

Obviously, the proposed framework is only a first step, and the potential impact and best way of applying each of these principles is not clear yet. Likely, it will be most suitable at the level of research planning and policy making, in particular with regard to biobanking and research directed at human genetic variation, as for example, the HapMap consortium. First results from HapMap II are available, and more distinct population subgroups will be included in ongoing research [18]. The availability and accessibility of comprehensive information from identified groups and communities raise questions that cannot be sufficiently dealt with by individual-oriented biomedical ethics. At this point, the proposed set of principles is crossing the boundaries of traditional ethics. Yet, very large-scale databases, after all, consist of individual data sets. The position of the individuals that make up the group remains unclear. Advancing technologies bring a rapid increase in scale, pace, and yield of information

content, thereby closing the gap between "anonymous" population research and personal genomics: both are "open" in the end.

18.9
Personal Genomes

No doubt, the year 2007 will be remembered, even beyond the biomedical research community, as the year of the personal genomes [19, 20], when the first personal whole genome sequences became available, one of them being the first human diploid genome [21, 22]. However, for both individuals so far only genotype data are publicly available and accessible at the NCBI Trace Archive [23]. In Summer 2007, at Harvard Medical School, the official launch of the first phase of the Personal Genome Project (PGP) took place in which 10 volunteers are involved, among them the PI of the project, George Church. At the next stage, a further expansion of the project is planned that may at some point in future include more than 100 000 volunteers [20].

18.9.1
What is a Personal Genome and What is New About It?

The term "personal genome" refers to a comprehensive genotype plus phenotype data set that, preferably, also contains information on environmental exposure and nutrition. A personal genome is by definition identifying and there is no way of ruling this out. Taking into account that any tiny piece of DNA information is identifying, it is obvious that any additional data reveal more about the individual they stem from. The American Society of Human Genetics says in its statement on GWAS:

> *[Being] acutely aware that the most accurate individual identifier is the DNA sequence itself or its surrogate here, genotypes across the genome. It is clear that these available genotypes alone, available on tens to hundreds of thousands of individuals in the repository, are more accurate identifiers than demographic variables alone; the combination is an accurate and unique identifier [24].*

This sets the scene for delineating the challenges to current ethical practices, in particular to the practice of promising privacy and confidentiality as a condition for obtaining consent.

Samples containing DNA are available in repositories since long, well before the advent of genome-wide association studies or the concept of personal genomes. Every clinical pathology collection constitutes a biobank and in combination with data from, for example, the medical records, "personal genomes" could easily be derived. However, such collections have quite different purposes. If people give consent, assurances of strict maintenance of confidentiality are among the standard conditions of the consent forms.

The same applies to the clinical research setting where voluntariness, consent, and a favorable risk–benefit ratio to study participants are essential criteria. Promises of

protecting privacy and maintaining confidentiality – up to complete anonymity – is the rule, any deviation from it needs thorough justification. Individual research participants will likely have an image in mind that differs considerably from the realities of biomedical research, where, for example, data sharing is part of good research practice and required by oversight bodies and funding agencies [25].

Complex procedural and statistical measures are employed to keep the data deidentified. Goals are protecting the privacy and confidentiality, respecting the autonomy of the sample donors, and protecting them from harm that could arise from use of the data. The strategy is in full accordance with the requirements of the protection paradigm of modern biomedical ethics.

18.9.2
But, Can Making Promises that Cannot be Substantiated be Ever Morally Justifiable?

Turning toward the reality of dealing with data having rich information content, in an increasingly wired world, we cannot ignore that "Hippocratic confidentiality" is merely an ideal image, which even in face-to-face clinical practice no longer exists.

Efforts for privacy protection can be made, but even when they work well strict confidentiality and anonymity cannot be guaranteed. Examples of violation of privacy and breaches of confidentiality are abundant, and occur in spite of data protection measures in all areas of modern life [26]. Moreover, there is increasing evidence from both fields of medical informatics and statistics that even the most advanced anonymization techniques are vulnerable to attacks. The recently developed strategy of k-anonymization that is used in, for example, IBMs "Hippocratic Database," has already been challenged by the technique of so-called l-diversity, which is claimed to be more robust [27, 28]. But the next attack is likely around the corner and we are certainly on the safe side when assuming that anonymization is impossible. We should therefore refrain from promises and making confidentiality a condition in consent.

Sacrificing the promise of confidentiality seems like giving up the moral foundations of biomedical research. At this point, the boundaries of the established ethical frameworks are about to be transgressed.

18.10
The Personal Genome Project: Consenting to Disclosure

The basic assumption of the Personal Genome Project that was developed alongside with the 2003 Harvard CEGS–MGIC proposal aiming at ultralow-cost/high-precision genomic imaging technology is that maximum comprehensive genotype–phenotype data sets are needed to obtain meaningful results in hypothesis-free, systems biology-based research [29, 30].

Fully consented data sets are needed from volunteer participants to make this research justified. Taking into account that secure anonymization is not possible,

the only consistent conclusion is that full and valid consent implies the abandonment of any of the conventional "confidentiality" clauses in the informed consent procedure.

In the "open consent," as designed for the PGP, *veracity* has been determined as the lead principle. Veracity is a necessary, though not sufficient, condition for autonomy and thus for valid consent. The PGP remains, in this respect, within the boundaries of the established moral concepts.

But, what does it mean to abandon the language of confidentiality clauses? What is it that prospective research participants positively consent to? At this point, open consent implies consenting to disclosure. Volunteers agree with full and public disclosure of their comprehensive data set, consisting of genome sequence data and extensive phenotype information, including data from personal health records and facial photographs. The comprehensive data sets may or may not be made publicly accessible.

In choosing this novel consent model, the Personal Genome Project clearly moves beyond the boundaries of established practices in research ethics. The concept will further evolve, as the next-generation sequencing technologies will do. One of the great assets of the open consent protocol is that it is open to all to watch and comment upon.

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3.

Shifting trends in ethics

Lunshof JE . Personalized medicine: new perspectives – new ethics?
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PERSPECTIVE

Personalized medicine: new perspectives – new ethics?

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Are new concepts in biomedical ethics required to keep pace with the developments in post-Human Genome Project (HGP) genomics? This paper traces the place of ethics in the post-HGP landscape. The need for a revision of the approach taken by biomedical ethics toward questions in genomics has been appreciated for years. Traditional biomedical ethics, led by the protection paradigm, was devised to serve a very different context. Today, compelling ethical questions arise from the tension between individual and collective interests in the context of population-based data collection and research. The collection of phenotype data, and the development of new sequencing technologies, raises burning questions that call for innovative tools and models in ethics. Future developments that will likely include the routine availability of personal genome information, and the advent of systems biology as a framework for interpretation, will require ongoing flexibility and a creative approach.

Do we need new concepts in biomedical ethics to keep pace with the developments in genomics, or should we tailor genomics and its applications, for example pharmacogenomics, to fit within our current ethical framework?

The need for a revision of the approach taken by biomedical ethics in questions concerning genomics has been appreciated for years [1,2]. However, no significant changes are so far apparent. Developments in ethics are slow compared with the fast-moving dynamic of genomics. Among the vast range of challenging questions in the field of research ethics and genomics, the problem of ethics as an impediment to research is a particularly burning issue. Three aspects with direct relevance to research in pharmacogenomics and pharmacogenetics should be mentioned here. First, the traditional content of medical ethics and its guiding principles cannot always adequately respond to the burning questions posed by genomics research. Traditional medical ethics was conceived for dealing with a different type of questions. The principles that are applicable in the context of protecting individual research subjects in clinical trials may not be appropriate for dealing with questions that arise in the context of biobanking or of genotyping for pharmacogenetic purposes. Second, the way in which ethics is mainly being practiced by the ethics profession – 'ethics as usual', as a *Nature Genetics* editorial calls it [1] – the application of philosophical theory to a clinical or research question – is perceived as providing too little pragmatic moral guidance. It does not live up to the expectations of the international community of scientists, giving rise to disappointment and frustration [1]. Increasing rigidity in research review and governance procedures is a further cause of discontent [3,4]. Notably, in clinical research and in large-scale epidemiological studies in genetics, the process of ethics review is perceived as increasingly impeding research and in some cases inhibiting its initiation due to complicated and extremely time-consuming procedures [5–7].

Difficult questions arise: what has made ethics become such an obstacle? Is this inevitable, while inherent to the critical stance that ethics is supposed to take? And with regard to research ethics: must ethics be a prohibitive instrument, or can it be critical and yet provide constructive tools? This should not be understood as disparaging ethics, but rather as an attempt to revitalize it.

This paper traces the place of ethics in the post-Human Genome Project (HGP) landscape, with focus on some issues with immediate relevance to personalized medicine. The concise survey will cover: a note on personalized medicine, the context of current and future ethical issues, some examples of the questions at stake and the current ethical approaches toward these questions. The outlook will point to the need for innovative tools and strategies as, given the intrinsic dynamic of developments in genomics, the greater challenge for ethics foreseeably lays ahead, awaiting in-depth research into creative solutions.

Keywords: altruism, equity, ethical principles, future perspectives, Human Genome Project, personalized medicine, Personal Genome Project, pharmacogenomics, research ethics

future medicine

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As mentioned previously, research governance procedures and structures are also major obstacles to efficient research. However, they will not be dealt with in the context of this paper.

Personalized medicine

First, a remark on personalized medicine, as the notion as such has been disputed. The practice of medicine is personalized by definition, as it aims to meet individual needs by seeking to provide the optimum treatment for individual patients [8,9]. Therefore, personalized medicine may not seem to be a new or revolutionary concept at all, it may even appear to be a tautological notion. In this paper, personalized medicine refers in the first place to pharmacogenetics-based individualized pharmacotherapy. However, taking into account the current developments in genomics, it indirectly also refers to possible future models of personalization, as for example nutrigenomics, and other individual-adjusted interventions resulting from insights in proteomics, metabolomics, and the further development of systems biology.

Current, short-term & future issues

Today, ethical questions related to pharmacogenomics predominantly arise in the context of research and policy making, including regulation and oversight. Drug development, and in particular clinical trials, have always been areas of serious ethical, legal and social concern. Due to the very nature of research, this will remain so in the near and distant future. Due to the current low level of implementation, pharmacogenetics does not yet raise major ethical dilemmas in clinical practice. However, this may change in the near future when genotype testing and pharmacogenetics-based pharmacotherapy become part of the standard protocols for the treatment of common diseases. Currently, clinical application has been established in certain areas of oncology [10–12], and it is almost ready for use in other areas, such as psychiatry and internal medicine [13–15].

However, personalized medicine is still in its infancy [16,101]. Genotype-adjusted prescribing of certain drugs that are metabolized primarily by cytochrome P450 (CYP) enzymes is feasible today, and although both conventional and microarray-based genotyping techniques are available for the identification of individuals who are at risk of adverse drug reactions (ADRs), its concrete implementation in routine clinical practice is lacking. From a moral point of view this is a reason for serious concern, as individuals continue to be exposed to ADRs that can be potentially avoided, while the knowledge and diagnostic means for improving drug safety by improved individual adjustment of prescribing are available [17]. On the other hand, the lack of broad clinical application means that potential ethical dilemmas have not yet become apparent. Implementation in the near- and medium-term future will likely confront us with a range of moral problems, some of which become visible already at the translational stage, the justification of eligibility for treatment with trastuzumab (Herceptin®) being a recent example [18–20].

In the distant future, when the availability of individual genome sequences becomes a reality [21,22,102], personalized medicine will extend far beyond pharmacotherapy, and the complexity of the resulting treatment decisions and of dealing with the personal genomic data sets involved is likely to give rise to yet unknown ethical dilemmas.

Questions at stake

Do pharmacogenomics or personalized medicine confront us with any new ethical questions? Even if many of the basic issues raised are very familiar to us – as they are intrinsic to healthcare delivery, healthcare regulation and policy, and biomedical research – some very specific ethically relevant questions arise. For example, issues in post-HGP genomics and pharmacogenomics that raise ethical concern include:

- Personalized medicine by definition addresses individual needs. Today's pharmacogenomics and pharmacogenetics research relies heavily on stratification, thereby focusing on groups. In drug development research genotyping is widely used. However, as individual genotyping is not yet feasible in clinical practice and reliable data on phenotype/genotype associations are lacking, certain easily observable phenotypic traits, such as skin color, tend to be used as a proxy for genotype. This can be to the disadvantage of individuals who do not have the 'expected' genotype and, depending on the diseases and treatments a stake, it can be stigmatizing for certain groups. The use of (self-identified) race, ethnicity, or ancestry as a proxy for genotype is highly disputed from the scientific and from the ethical, social and legal point of view [23–25].
- The collection of very large sets of data concerning genotype–phenotype associations is a necessary condition for the advancement of research in genomics [26,103]. This applies to

pharmacogenomics, but even more to research into the determinants of common multifactorial disease [27]. The collection of phenotype data in particular raises major concern about the protection of the interests of the individuals that are included [28]. Keywords are privacy and confidentiality, and the means for safeguarding that are various modes of de-identification, the option of withdrawal, strict limitation of access, storage, and use of data. However, these measures preclude optimum use of data and samples and seriously impede progress in research. Paradoxically, an obligation can be assumed toward the donors to make the best possible use of donated specimens and information.

Related issues are ownership of DNA and data, and consent for yet unknown future use of data and samples. Building the large data collections that are needed requires the willingness to share data among researchers from academia, as well as from the pharmaceutical industry. This altogether raises crucial questions of moral obligation [29].

Alternative concepts with great opportunities, but also great challenges for ethics, law and various social sciences' disciplines are:

- The exploration of the potential reservoir of 'health information altruists' within the general population [30]. The release of data from (future) patient-controlled electronic medical records for research purposes by the patient themselves, might offer a solution to many problems surrounding privacy and consent. However, it will raise many new questions as well.
- The Personal Genome Project (PGP) uses a similar approach: since January 2006 volunteers are being recruited who agree to the sequencing of their entire genome (or a part of it) and to placing their genotype and phenotype information in the public domain [21,102]. Apart from the scientific prospects, this project challenges all our current moral intuitions, in particular with regard to privacy, confidentiality and mutual obligations within families, and calls for new and creative approaches in ethics.

Finally, in the distant future, the establishment of approaches from systems biology in clinical practice will include the use of information based on so-called 'endophenotypes' [31]. Given the predictive potential of these parameters it will likely imply a come-back of ethical questions that are traditionally related to predictive and presymptomatic genetic testing.

Biomedical ethics – the traditional model

Can current approaches in ethics deal with the questions at stake in post-HGP genomics in a satisfactory manner?

We should never forget that our current twentieth century framework of biomedical ethics arose as a reaction to a dark past of crimes against humanity, of scandals and of medical malpractice [32,33]. Therefore it is no surprise that 'protection' is the key concept – and the leading paradigm of biomedical ethics is the protection paradigm. The prime object of protection is human dignity [34,104]. Among the values derived from this core notion is, as a primary value, the value of the life and bodily integrity of individuals which is conditional upon all other values, and secondary, the individual free will and the acknowledgement of the right to self-determination [35,36,105].

The classical principles of biomedical ethics comprise the well-known four clusters of norms that were first presented by Beauchamp and Childress in their seminal textbook *Principles of Biomedical Ethics* in 1979 [37] (**Table 1**):

- Respect for autonomy (respecting the decision-making capacities of autonomous persons)
- Nonmaleficence (avoiding the causation of harm)
- Beneficence (norms for providing benefits and balancing benefits against risks and costs)
- Justice (norms for distributing benefits, risks and costs fairly)

These principles were primarily intended for moral guidance of relationships between individual actors in therapy and research. In the context of research this model gives rise to the fundamental requirements of informed consent, voluntary participation free of undue constraints, a favorable risk–benefit ratio for participants, and the right to withdraw at any time from a study without consequences for medical care, to mention the most prominent ones [34]. In the broader context of research within populations or specific communities, this means safeguarding a just distribution of burdens and benefits for the members of the community, and great scrutiny in setting the criteria for fair subject selection. Ethical review of the fulfilment of these requirements and Institutional Review Board approval of study protocols are the central procedural elements in any type of research.

When looking at post-HGP drug development research and pharmacogenomics, and the way in which populations and communities are involved, we are confronted with the limitations of an ethical framework that by tradition focuses on

Table 1. Ethical principles.

Classical principles	Early-HGP	Post-HGP
Beauchamp and Childress 1979 [37]	Knoppers and Chadwick 1994 [43]	Knoppers and Chadwick 2005 [38]
Respect for autonomy	Autonomy	Reciprocity
Nonmaleficence	Privacy	Mutuality
Beneficence	Justice	Solidarity
Justice	Equity	Citizenry
	Quality, as owed to human dignity	Universality

HGP: Human Genome Project.

relations between individuals, and assumes a clear set of commonly shared core values and principles. In how far can it be applied to situations where the interests of individuals and groups or communities are in conflict, and where no consensus exists on core values and shared principles?

Research ethics: new concepts

In a recent article, Knoppers and Chadwick argue for the need of a shift in emphasis of the principles that make up the normative framework of research ethics, with focus on research in human genetics in particular [38]. Such a shift in emphasis of ethical principles does not imply disqualifying or discarding of the old ones, nor does it mean giving up core moral values. However, the authors do hold the view that " … ethical thinking will inevitably evolve as science does", and that "there might not, and cannot, be universal norms in bioethics, as emerging ethical norms are as 'epigenetic' as the science they circumscribe." A view that I would share. However, the issue of the universality of norms touches upon the most fundamental questions of ethics that will always be hotly contested and cannot be once and for all resolved by rational discourse [39]. The professional debate surrounding the recent United Nations Educational, Scientific and Cultural Organization (UNESCO) Declaration on Bioethics and Human Rights [105] shows the broad spectrum of views – that are all sustained by highly plausible arguments – on the key issues of ethical relativism, universality of norms and conflicting values [40–42].

Knoppers and Chadwick show the evolvement of norms from the early-HGP to the post-HGP era. In a 1994 article in *Science* they identified five basic principles underlying international consensus on the need for harmonization of national regulation on topics related to human genome research. These five principles are: autonomy, privacy, justice, equity and quality out of respect for human dignity [43] (**Table 1**). The completion of the HGP has confronted us with a shift in emphasis in genomics research that can be characterized as a shift from clinical genetics – in the early and mid-nineties – to population-directed research genetics, carried out in projects of formerly unknown dimensions and including populations and researchers on a global scale. New ethical principles that are being proposed by Knoppers and Chadwick are in keywords (**Table 1**):

- Reciprocity (exchange of information between researches and participants; transparency, also concerning possible commercialization)
- Mutuality (genetic information and DNA as family-property – risk sharing within families)
- Solidarity (a willingness to share information for the benefit of others; common interests or interests in common)
- Citizenry (public involvement with science [policy]; genetic heritage and collective identity)
- Universality (the human genome as a shared resource; common heritage of humanity; obligations to future generations and benefit sharing)

However, the proposed framework is only a first step and the potential impact and field of application for each of these principles is not yet clear. The single principles are interrelated and in part overlapping, and further research is needed. The concrete burning questions in the field of genomics research should be the starting point and test case for this investigation. Other sets of principles have been suggested, as for example privacy, sovereignty and justice [44]. The principles mentioned are not mutually exclusive, but rather complementary. A common feature of the various new approaches is the foundation in the modern western world, so-called 'principlist' biomedical ethics. Its validity as a set of principles that is reconcilable with moral values and frameworks globally is a much debated question in bioethical theory.

Equity

The principle of equity is likely to be a key concept in any framework of research ethics, as it is at the foundation of distributive justice. A new model of genetic equity has recently been put forward as a line of protection for the rights of the individual and as a safeguard for human dignity in the context of genetics [45]. However, the lack of clarity of the concept of human dignity has been criticized, as well as its dubious use as an instrument of constraint in regulation and science policy [46]. The greater promise of the principle of equity seems to be its use in a theory of distributive justice as applied to questions related to equality and justice in not-individual-oriented genomics.

Altruism

The concept of Health-Information Altruism was recently introduced by Kohane and Altman [30]. Starting from the huge privacy and confidentiality problems surrounding large scale phenotype data collection, they suggest a turn toward the voluntary public sharing of health data by fully informed and highly motivated individuals. These volunteers could be described as 'information altruists'. With the advent of personally controlled electronic health records, individuals would be in a position to decide for themselves what parts of information they want to disclose, and in this way various degrees of information altruism will be possible.

The proposed concept can be morally founded on various types of ethical theory. Altruism may, by definition, belong in the realm of virtue ethics, but other types of ethical theory could offer a plausible justification as well. In any case, this concept deserves very serious consideration, as it could mean a truly innovative step in ethics, as well as in post-HGP research aiming at personalized medicine.

New genomics, innovative ethics: in search of tools

How can these concepts and principles be turned into tools of a critical, but constructive ethics? Their implementation should fit the current and future burning issues and make a substantial contribution to facilitating progress in genomics with the outcome of improved pharmacotherapy by genotype-adjusted drug prescribing as a near-term goal, and the realization of a comprehensive model of personalized healthcare in the long term. These goals are to be set not only at the individual level and in the developed part of the world, but also at the level of public health, including the public health in developing countries. Meeting the needs of patients with rare diseases by making the required orphan drugs available, is a further global goal.

To realize these goals, a normative framework with an appropriate content is required in the first instance. The proposed set of principles described above could be a starting point for formulating a limited set of very clear, concise, understandable and broadly applicable criteria for testing the moral acceptability of genomics research. This is a task for the ethics' profession. The concepts of genetic equity and of health information altruism deserve very careful analysis and further research.

In addition to the innovative content, new procedural tools are required that can contribute to streamlining the ethics review procedures, reducing redundancies, promoting transparency, and harmonizing regulation. However, these goals may not be easy to accomplish, as hierarchies of committees, agencies and authorities have been established during the past decades, a development that cannot be reversed simply.

Box 1 provides a schematic overview of ethics in perspective.

Outlook

The huge field of post-HGP genomics is developing according to its very own dynamics. Personalized medicine may be one of the end points, and pharmacogenomics is a part of it. Current complaints regarding the role that ethics plays refer to research ethics review in particular. Ethics review procedures in clinical research deserve serious attention to reduce the risk of harm to patients and research subjects caused by undue delay of studies, a goal that can be already accomplished today. The traditional principles of biomedical ethics that require avoiding the causation of harm and, when applied to research a favourable risk–benefit ratio for research participants, should provide sufficient grounds to combat current procedural delay.

Resolving the dilemmas that arise from stratification as a methodological approach in pharmacogenomics is far more difficult. As long as no cheap, quick and easy diagnostics are available that allow for routine genotyping, the use of group-based proxies such as gender, ancestry, ethnicity – either self-identified or ascribed by the healthcare professional – will be the next-best option. In clinical practice this means that individuals with 'orphan' genotypes will pay the

Box 1. Ethics in perspective.

Antiquity till present

Traditional medical ethics:

- Actors: individual patient – physician
- Features: traditional personalized medicine; paternalism; unequal balance of power
- Ethics content: virtues; *primum non nocere*; privacy; confidentiality; respect; trust
- Ethics procedures: professional codes of conduct

Clinical research ethics:

- Actors: individual patients/healthy probands – researchers (physicians) – industry
- Features: protection paradigm; aggregation of data; beneficiaries?
- Ethics content: human dignity; voluntariness; informed consent; rights & duties; risk–benefit ratio; return of research results? [47]
- Ethics procedures: ethical review; research governance review

Genomics research ethics:

- Actors: groups (consisting of individuals) – researchers (scientists; physicians)
- Features: stratification; large-scale data aggregation: biobanking; coding of data and samples; data sharing; beneficiaries?
- Ethics content: individuals *qua* group members; 'donation' of data and samples; altruism?; return of research results? [47]; equity; distributive justice
- Ethics procedures: ethical review; research governance review

Future

Postgenomic medical and research ethics:

- Actors: individuals – families – physicians – scientists (bioinformatics)
- Features: systems biology-based treatment approaches aiming at personalized preventative medicine; personally controlled electronic health records; aggregation of individual data; individuals as complex systems; multiple phenotypes within each system; endophenotypes: predictive potential; public health implications
- Ethics content: sharing within families? – mutuality – solidarity; privacy vs disclosure: issues of traditional medical ethics; beyond paternalism?; balance of power?; distributive justice, within societies, between nations
- Ethics procedures: ethics review; research governance review; new structures?

morally painful, but inevitable, price. A set of ethical principles tailored to address these dilemmas could help to improve the quality of decision making in study design, in drafting regulatory guidelines, and in short-term public health policy. Securing acceptability to the society concerned, and taking into account cultural diversity – without slipping into crude relativism – are major conditions for successful implementation. The ethics' profession is called upon to become pro-active here.

It seems that scientists are currently taking the lead in ethical innovation. While techniques for cheap, quick and easy genome sequencing are being developed, at the same time the feasibility of appealing to altruistic motives for sharing very personal information are being explored, on the initiative not of ethics' professionals, but of scientists with strong moral intuitions [30].

However, we need not fear the loss of our moral heritage. Moreover, innovative concepts in bioethics will build on the global reservoir of moral tradition, and certain long-term developments in science, as for example, the establishment of the paradigm of systems biology, might in 30 years bring back to us the problems and the principles of the ethics of mid-twentieth century genetics.

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Highlights

- Biomedical ethics needs revision in order to be able to keep pace with the developments in genomics.
- Ethics is increasingly perceived to be impeding research.
- Discontent arises from: ethics content, ethics procedures, and practice of 'ethics as usual'.
- 'Personalized medicine' will, in future, extend far beyond pharmacogenetics and pharmacogenomics, the scope of ethical dilemmas will increase.
- New sets of principles have been proposed, but they are at the translational stage and not yet ready for application – innovative ethics research should be the first priority.
- New tools are needed: a limited set of criteria for testing the moral acceptability of genomics research. Criteria must be clear, concise, rationally understandable and globally applicable.
- Scientists are currently taking the lead in ethical innovation. Even if we assume that 'ethics evolves as science does' [38], the ethics' profession is called to action.
- Innovative concepts in ethics will build on the global reservoir of moral tradition.
- Scientific developments in the far future may bring us back to old problems and the need to rely upon classical solutions.

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Genomics for all: ethical implications for clinical practice

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EDITORIAL

Hippocrates revisited? Old ideals and new realities

Jeantine E. Lunshof · Ruth Chadwick · George M. Church

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Abstract Individual genomics has arrived, personal decisions to make use of it are a new reality. What are the implications for the patient–physician relationship? In this article we address three factors that call the traditional concept of confidentiality into question. First, the illusion of absolute data safety, as shown by medical informatics. Second, data sharing as a standard practice in genomics research. Comprehensive data sets are widely accessible. Third, genotyping has become a service that is directly available to consumers. The availability and accessibility of personal health data strongly suggest that the roles in the clinical encounter need to be remodeled. The old ideal of physicians as keepers of confidential information is outstripped by the reality of individuals who decide themselves about the way of using their data.

Keywords Patient–physician relationship · Confidentiality · Personal genomics · Genotyping · Data sharing · Direct-to-consumer services

It used to be the pharmaceutical industry approaching you, seeking probands for clinical trials among your patients, and it used to be researchers from academia seeking subjects for biomedical and social sciences' studies, and recently, it could be a population biobank project notifying you of your patient's enrollment and her authorization to access her medical records that you are keeping.

Today, it may happen that you are approached by one of your own patients, that you have been treating for years, asking you to make the data from her medical record available, as she intends to contribute these to an open individual genomics project that collects comprehensive genotype and phenotype data.

Individual genomics is there, personal decisions to make use of it are a new reality (Editorial 2008). As a doctor, what should you do?

There are the legal issues surrounding the ownership of medical data that in many countries resides with the patient. But how about that other part of your relationship with your patient—the issues of mutual trust, confidentiality, and protection of privacy?

The combination of health-information altruism (Kohane and Altman 2005) and self-management by individuals of their medical data beyond the assumedly safe domains of the physician's office and the approved clinical trial seems to undermine the traditional ideal of Hippocratic confidentiality. Many physicians will find the request like that of the patient mentioned above, utterly disturbing. Besides, complying with it may be quite time consuming. We will argue that the traditional Hippocratic ideal has in fact been superseded quite a long time already.

In practice, one-to-one strict confidentiality between doctor and patient is the exception rather than the rule, as the clinical encounter will always include third parties as well. In research, by industry-based or academic researchers, the promise of confidentiality often constitutes a key condition for consent. It is assumed that this promise can be fulfilled through

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measures of data protection. However, it becomes ever more obvious that absolute data security does not exist. Ethical and legal frameworks for the conduct of human subjects research must take into account that strict confidentiality is not a promise that can be delivered upon. We will give three examples of factors that call the widely held concept of confidentiality in the medical context into question.

First, the flaws in the strategies and the tools used to protect identity and information content of participants in research.

In the past decades comprehensive regulatory frameworks have been established for the protection of personal data. Guidelines for research protocols pay a great deal of attention to describing different modes of coding—e.g., single coded, double coded, and anonymized—in order to ensure the separation of individual identity from information content in data sets. Both in clinical trials and in epidemiological research there has been a strong focus on control of the keeper of the key of the code and on conditions for access, stating under what circumstances the key may be released. The normative framework of ethics and law has addressed exactly this: the actors and the rules. Providing guidance to those conducting research is among the core business of normative ethics and this involvement is to a large extent institutionalized in form of committees, advisory groups, oversight bodies, and the like. In the review process relatively little attention has been paid to the quality of the keys: how reliable are they? Research in medical informatics and statistics has shown that security is often illusory, discussion with patients and research subjects of data protection should acknowledge this (Malin 2005).

Second, the practice of data sharing leads to a further distortion of the ideal image of confidentiality.

Large-scale genomics research confronts us with studies using increasingly comprehensive genotype and phenotype data sets that are being shared among researchers and that often are publicly accessible. Moreover, DNA is an identifier in itself. In this situation, the keepers of the keys to individual identity are applying old rules to new cases. Transporting the traditional idea of confidentiality into the protocols of large-scale genomics research and biobanks, is misleading. The accessibility of data in a databank will become the endpoint of a chain of unsustainable promises of privacy and confidentiality that once started with the Hippocratic ideal in mind, in a doctor's office (Lunshof et al. 2008). The same holds true for clinical trials: they differ in scale, but data are being shared and allow for reidentification. Remaining silent on this point may cause irrevocable damage to trust in science and researchers. Indeed, study protocols and consent language increasingly include paragraphs on data sharing.

Third, genotyping has become a service that is available directly to consumers. Making use of these easy accessible web-based services is a strictly individual decision, like the purchase of any product or services via internet. However, be it for genealogical, ancestry, or paternity testing, for nutrigenomics or pharmacogenomics purposes, or susceptibility testing for serious hereditary disorders, the client hands over body material and personal information. Both would be regarded as subject to strict confidentiality in the patient–physician relationship.

Obviously, individuals, as patients or assumed healthy consumers do have sufficient confidence in the standards of confidentiality as advertised by the service providers. But, being their own doctor you may get involved as well with their course of action. This will often occur at the end, when patients present you with the test results and seek "medical direction" (Hunter et al. 2008). However, you might get involved at the beginning, as in our case, when a patient asks you to be a facilitator of her decision to engage in research that will make its yet unpredictable findings available, together with previous medical data, not only to herself but to an undefined research community, and in open access studies also to the public at large.

In this new context, mutual trust is the basis for giving up confidentiality and privacy protection. With blurring boundaries between the clinical, the research, and the commercial domain, the roles in the clinical encounter likely need to be remodeled. Direct involvement of individuals in research, through interactive researcher–subject communication may increase transparency and take a burden off the patient–physician relationship. Modern information technology has the tools for direct communication ready at hand. However, in a wired, web-based world individuals should be aware that any personal data that they release—informing about their lifestyle, opinions, or health—may be used for drawing inferences that are very detrimental to their lives. This may happen, regardless of whether the data have been made available altruistically, in good faith, or out of sheer naivety. Society can try to regulate the use of health related and genetic data. But, informing people of the potential impact of their own decision to go public with their personal data will likely be the first huge challenge beyond the traditional protection of privacy and confidentiality.

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New roads to consent. In search of pragmatic moral guidance

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PERSPECTIVES

SCIENCE AND SOCIETY

From genetic privacy to open consent

Jeantine E. Lunshof, Ruth Chadwick, Daniel B. Vorhaus and George M. Church

Abstract | Recent advances in high-throughput genomic technologies are showing concrete results in the form of an increasing number of genome-wide association studies and in the publication of comprehensive individual genome–phenome data sets. As a consequence of this flood of information the established concepts of research ethics are stretched to their limits, and issues of privacy, confidentiality and consent for research are being re-examined. Here, we show the feasibility of the co-development of scientific innovation and ethics, using the open-consent framework that was implemented in the Personal Genome Project as an example.

Current developments in genomics challenge the established framework of biomedical ethics because the empirical facts of the genomic science change too fast for the reflections of ethics to keep pace with. At the same time, as practical applications of new technologies are being developed, scientists call for pragmatic moral guidance[1]. Recent revelations about the human genome, such as the abundance of copy-number variation (CNV)[2], and the large-scale identification of functional elements through the Encyclopedia of DNA Elements (ENCODE) project[3] pave the way to a new understanding of human genome function. The number of published genome-wide association studies (GWAS) continues to rise quickly. Newly developed technologies, in particular high-throughput, low-cost sequencing[4,5], are being applied to increasingly large human genome and phenome data sets. These developments have ethical, legal and social implications that call for strong cooperation between science and humanities[6]. While looking for approaches that can adequately address the moral and policy issues that are raised by emerging genomic technologies, ethicists are increasingly aware of the need for a shift in emphasis, even if it ultimately requires revision of key concepts in mainstream biomedical research ethics.

One component of traditional medical ethics — the obligation to confidentiality — has recently come under review. In addition to its implementation in the clinical setting and in the context of public health, the applicability of confidentiality to large-scale genomic research now calls for attention. Developments in both medical informatics and bioinformatics show that the guarantee of absolute privacy and confidentiality is not a promise that medical and scientific researchers can deliver any longer[7,8]. This has concrete implications for the validity of consent for participation in research. Consent is relevant in building large-scale databases containing genotype data that are inevitably traceable to individuals, as well as in generating 'personal genomes'. What pragmatic moral guidance can be offered under these new circumstances?

In this article we argue that the reality of the new genetics and genomics urges us to abandon the traditional concept of medical confidentiality. As we hold the view that ethical thinking evolves alongside science[9], we argue that new models are needed to offer robust moral guidance while keeping the reality of a dynamic science in mind. One such new model is the open-consent approach, developed in the Personal Genome Project (PGP). We take this example to illustrate the feasibility of the co-development of ethics and genomics in a specific study protocol. We focus on the quality of consent to participation in studies using correlated genotype and phenotype data.

> "…new models are needed to offer robust moral guidance while keeping the reality of a dynamic science in mind."

Genetic privacy

The emergence of genetic privacy. Genetic privacy usually refers to informational privacy[10]. It indicates an individual's right — one that is perhaps extended to families and communities — to protection from non-voluntary disclosure of genetic information. This concept emerged over the last few decades, as a consequence of developments in genetics and information technology. What made the rise of this concept possible was the disclosure of the 'invisible' part of heredity at the molecular level, prior to which the information about hereditary traits was limited to what could, in principle, be known to others — such as individual and family health history (even if certain diseases running in the family were kept as a family secret), pedigree information and obvious physical traits. More recently, rapid advances in sequencing technologies are making fast and affordable whole-genome sequencing readily available, and developments are continuing to accelerate[11,12,13]. Comprehensive data sets to establish informatics links among ten thousand to a million human genome sequences and extensive phenotype analyses are needed to effectively generate and test hypotheses, but they also enable the identification of the individuals whose DNA sequences they contain. This puts the validity of the existing consent protocols into question. If promises of privacy and confidentiality need to be abandoned, what are the implications for meaningful consent in the context of genomics research?

Genetic privacy can be taken to denote a particular instance of the general concept of privacy, although often it is used as a value-laden concept that is qualitatively different from 'normal' privacy[14] — a concept that presupposes adherence to genetic exceptionalism[15]. By contrast, we subscribe to the view that genetic privacy is just one instance of privacy.

Before turning to the general notions of privacy and confidentiality and their relevance to the process of consent, we describe the increasing inadequacy of health information protection against the background of the historical development of information technology and its application for epidemiological purposes.

Health information privacy. The new methods of data storage that were introduced to many hospitals in the 1960s and early 1970s allowed electronic searching and linking[16]. This, combined with a growing emphasis on individual rights in medical ethics and health law, highlighted the need for the protection of 'health information privacy'[17]. Since then, the increasing opportunities to gather genetic information about individuals have raised concerns among the public and the policy makers about access to this type of information and its potential abuse. The experience with sickle-cell anaemia screening in the United States demonstrated,

as early as 1972, that stigmatization of individuals on the basis of their membership of a particular group is a real risk[18]. Whether this is based on genetic or other traits, conventional individual privacy protection misses the point. It does not work in the case of so-called non-distributive generalizations about groups in which the individual profile is indiscernible from the group profile, as is the case in epidemiological research. The concept of 'categorical privacy' has recently been proposed to overcome the inadequacies of traditional individual-centred concepts of privacy with regard to the individuals that make up the non-distributive profile of a group[19]. Current legislative efforts, such as the Genetic Information Nondiscrimination Act in the United States, attempt to provide a certain level of protection, at least against the potential detrimental use of genetic data[20].

Box 1 | **Threats to privacy and confidentiality**

Actions that are aimed at uncovering identity

- Re-identification after de-identification using publicly available data, for instance, finding health records using publicly accessible administrative data (see REF. 58 for an example).
- Combination of surnames as well as genotype and geographical information, for instance, the tracing of an anonymous sperm donor by his offspring (see REF. 59 for an example).
- Inferring phenotype from genotype by identifying information in DNA and RNA, for instance, stature, hair or iris colour, or skin colour (see REF. 60 for an example).
- Any amount of DNA data in the public domain with a name allows for identification within any anonymized data set.
- Identification through the DNA of a first-degree relative, for example, the identification of Bernardo Provenzano through his brother's DNA[54].
- Identification by phenotype using imaging techniques for reconstruction of facial features.
- Hacking into computer systems.
- Physical attacks on encryption keys; for example, so-called cold boot attacks (see REF. 61 for an example).
- Theft or loss — by accident or forgetfulness — of a laptop or of data-storage devices.

Causes of disclosure of information content

- The increasing availability of aggregate data in public, private and state-controlled databases, including: clinical biobanks and databases; population biobanks and databases; research biobanks and databases with academia and industry; and forensic biobanks and databases.
- Data sharing and secondary use of data.
- Developments in technology, in medical informatics and in bioinformatics.
- Information technology accidents leading to security breaches.
- Actions driven by insatiable curiosity about self and others.
- The increased ease of finding electronic data with web-based search engines.

Privacy and confidentiality

Privacy is a complex notion. Genetic privacy refers to a specific field of application and is mostly used in the limited sense of informational privacy.

Informational privacy is concerned with the limits on access to personal information; confidentiality, anonymity and secrecy are branches of it[10]. Confidentiality implies trust in private and in professional relationships between individuals. The maintenance of confidentiality by professionals is vital to the trust in the profession, for example, to the public trust in physicians, lawyers or members of the clergy. Anonymity refers to a state of blocked or restricted access to information that identifies persons. Secrecy implies having control over the disclosure of information. It entails an aspect of intentional concealment and can also be deliberately used to the detriment of others[10].

Infringement of privacy. Privacy can be violated by forces that are beyond individual or institutional control, such as accidental data release, data release that is required by authorities, or by criminal offences, including burglary, hacking, hardware and/or data theft (BOX 1). Infringement of privacy can cause considerable material and immaterial harm: to social position and opportunities, to personal and familial status, and to self-image and perception by others. However, infringement of privacy need not relate to any moral failure.

In addition to the above threats to secrecy (BOX 1), there is increasing evidence from the medical and bioinformatics fields that indicates that absolute privacy and confidentiality is not a promise that medical and scientific researchers can deliver[7,8,21,22]. Malin and Sweeney have shown that re-identification of individuals is possible through genotype–phenotype inference, and through methods such as genealogical information, trail re-identification or so-called dictionary attacks[21]. A lot of effort is made to improve data safety. Recently, the statistic strategy of *k*-anonymization has been developed in which each relevant entity is hidden in at least *k* peers[23]. This strategy is used with strong reference to traditional confidentiality in, for example, IBM's Hippocratic Database Technology[24]. However, it has already been challenged by so-called *L*-diversity, which, according to its proponents, is more robust[25].

Breaching confidentiality. A breach of confidentiality implies an action on the part of those who are supposed to keep it. Therefore, in contrast to an infringement of privacy, it implies a moral failing by definition. Maintaining confidentiality, on the other hand, might protect one party from harm while exposing others to it. The paradigm case in medical ethics is the Tarasoff case[26], in which a psychiatrist failed to breach confidentiality to warn a young woman that one of his patients intended to kill her — this woman was subsequently killed by his patient. A 'duty to warn' persons who are directly at risk was derived from this case. Although there are dissenting opinions[27], it is widely agreed that the obligation of confidentiality cannot be absolute[28–30]. The World Medical Association adopted this point of view in its 2006 version of the International Code of Medical Ethics[31]. However, there is also a consensus that specific and weighty circumstances are required to justify a breach of confidentiality. In situations in which there is no threat to the life or well-being of third parties, patients are likely to expect strict confidentiality from their doctors. Therefore, when individuals donate samples and data originating from individual medical treatment for research, they might have unrealistic expectations about the degree of confidentiality that will be provided. This belief is reinforced through reassuring statements about 'strict confidence', contained, for example, in informational materials for research[32].

Recent research has shown that in regular general practice, there is also a considerable discrepancy between patients' expectations and the true extent of confidentiality available[33,34].

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Confidentiality, consent and disclosure. Awareness of the discrepancy between patients' expectations of confidentiality and actual practice is crucial when devising consent for research participation. These expectations are shaped according to the traditional image of exclusive patient–physician confidentiality. Thus, the perceived confidentiality of the setting in which patient information is generated is decisive. In addition, as Rothstein shows[35], there are three key time points with respect to confidentiality. First, the initial moment of sharing of confidential information; in the health-care setting, this is a direct consequence of the patient's decision to seek help. Second, the external disclosure beyond the confidentiality-based relationship when making data available for the purpose of research; explicit consent is needed. Third, the time of potential re-disclosure, for example, through data sharing or linking of data collections in the course of research, or when data that were coded at submission are re-identified. A crucial consideration is that consent for disclosure and re-disclosure is given only upon certain conditions; a key condition usually being the assurance of secrecy with regard to personal identity and information content. Yet, how can secrecy be promised when the sharing of data is not only foreseeable but is, in fact, intended? The promise of secrecy is a major part of our argument in support of the open-consent protocol, as introduced in the PGP.

Consent and re-consent. Both the UK Biobank and the initial International HapMap Project are examples of *de novo* data collections and, as such, offer the unique opportunity to clearly define terms and conditions of consent from the outset. Consent can be narrow and specified, broad, or blanket; blanket consent implies that there are no restrictions to the scope and duration of the consent[36]. Obviously, broad or blanket consent can never be fully informed[37]. Consent might include a further layer: the consent to be re-contacted and give re-consent, for example, when new information becomes available that is relevant to the research subject, or if further research is being considered[38]. However, including the option of re-contacting and obtaining re-consent implies, by definition, maintaining identifiability and traceability of research participants.

In February 2007 the US health-care provider Kaiser Permanente announced a Research Program on Genes, Environment and Health (RPGEH)[39] that collects data and samples for GWAS and will surpass the UK Biobank in size and scope. Participants are informed that linking of databases and data sharing among researchers is intended. A striking feature of this project is that, as a health-care insurer, Kaiser Permanente recruits the participants from amongst its members, that is, its own insurees, and uses the data that have been stored in its archives for almost four decades. This is a typical case of new research on extant data for which re-consent will be sought. A preliminary survey, performed by the RPGEH, showed a great willingness to participate. Remarkably, this is in spite of the fact that a serious breach of confidentiality occurred at Kaiser Permanente in 2004, caused by a complex accident in its information technology structures[40].

Box 2 | **Key features of the Personal Genome Project**

The Personal Genome Project aims to build a framework for the development and evaluation of personal genomics technologies and practices at increasing scales. Its key feature is the comprehensive approach towards:

- The development of a broad vision of how personal genomes can be used to improve the understanding and management of disease.
- The development of technologies to improve the affordability of personal genome sequencing.
- The development of tools for interpreting genomic information and correlating it with the individual medical and biological information.
- The development of educational and informational resources for improving general understanding of personal genomics and its potential.
- The fostering of dialogue with research communities, industries, and public and governmental bodies involved with personal genomics and the related ethical, legal, and social issues.
- The development of a normative framework that addresses the needs of personal genome research in the context of open access to comprehensive identifiable genetic information.
- The implementation of this approach in interactive research on human subjects involving individuals who consent to obtaining and openly sharing their genome sequences and their related phenotype information.

The above points are adapted from the mission statement of the Personal Genome Project.

False promises, wrong expectations. The language for consent to participation in large-scale studies that require the collection of genotype and phenotype data hardly differs from the traditional consent protocols used in the clinical setting: it emphasizes the protection of privacy and confidentiality. For example, the consent form of the International HapMap Project assures the participants in the following way: "… it will be very hard for anyone to learn anything about you personally from any of this research because none of the samples, the database, or the HapMap will include your name or any other information that could identify you or your family."[41].

The HapMap informed-consent protocol does not unambiguously guarantee anonymity or confidentiality of participants' genetic information. On the contrary, it even mentions the risk of tracing identity through publicly available HapMap data. Nevertheless, the consent protocol clearly suggests that the risk of re-identification is vanishingly small.

The information leaflet of the UK Biobank explains to the volunteers that: "Only if you … give your written consent would we be able to access your medical records. (All such information would be kept in strict confidence.)"[32].

The data from the available literature are not unequivocal about how many research subjects would withhold consent without the explicit or implicit promise of confidentiality and anonymity. A large survey by Canadian researchers revealed that patients want to be actively consulted and give consent for their personal information to be used for research. The patients, however, make little distinction between identifiable and non-identifiable information[42]. Yet, other studies found that a substantial number of patients do not consent to data collection for research purposes from their existing records[43,44].

Non-valid consent. The finding that the confidentiality of genetic data cannot be guaranteed suggests that a research participant's consent might not be valid when it is conditioned on the assurance or even the unchallenged expectation of full genetic secrecy.

At the same time, large correlated sets of comprehensive genetic information are needed for GWAS that aim to uncover genetic determinants of common, complex human disorders[45,46]. Understanding of biological processes requires integration of diverse types of data. Applying systems-biology

Box 3 | **Key features of the Personal Genome Project's open-consent policy**

Open consent as part of the Personal Genome Project implies that research participants accept that:

- Their data could be included in an open-access public database.
- No guarantees are given regarding anonymity, privacy and confidentiality.
- Participation involves a certain risk of harm to themselves and their relatives.
- Participation does not benefit the participants in any tangible way.
- Compliance with monitoring of their well-being through quarterly questionnaires is required.
- Withdrawal from the study is possible at any time.
- Complete removal of data that have been available in the public domain may not be possible.

The moral goal of open consent is to obtain valid consent by effectuating veracity as a precondition for valid consent and effectuating voluntariness through strict eligibility criteria, as a precondition for substantial informed consent.

approaches to integrated personal data sets will facilitate the development of new modes of individually targeted treatments or disease prevention[47,48]. However, anything approaching a comprehensive genotype or phenotype (including molecular phenotypes) ultimately reveals subjects' identities as surely as conventional identifiers such as a name and social security number would. The American Society of Human Genetics (ASHG) declares the following in a statement on genome-wide association studies: "[the ASHG is] acutely aware that the most accurate individual identifier is the DNA sequence itself or its surrogate here, genotypes across the genome. It is clear that these available genotypes alone, available on tens to hundreds of thousands of individuals in the repository, are more accurate identifiers than demographic variables alone; the combination is an accurate and unique identifier."[49].

These facts fundamentally challenge current consent practices, ones that strongly suggest or even assure strict confidentiality, in otherwise carefully designed genetics and genomics projects, as illustrated by the HapMap and the UK Biobank. Thus, when applied to GWAS, common and widely used consent practices might in fact result in disingenuous consent, at least insofar as they are based on untenable promises of privacy and confidentiality[50].

Personal genomes, open consent

How can full or at least substantial[51,52] informed consent for participation in GWAS be realized? What are the requirements of a study design and a consent protocol that abandon confidentiality in order to preserve trust? Should veracity precede autonomy?

We believe that the building of any comprehensive genotype–phenotype data collection requires that the individuals from whom these data are derived be fully aware that the data can be and likely will be accessed, shared and linked to other sets of information, and that the full purpose and the extent of further usage cannot be foreseen. Individuals should realize that they are potentially identifiable and that their privacy cannot be guaranteed. Full and valid consent by the participants requires veracity on the part of the researchers, as a primary moral obligation. Below we describe an open-consent model and its practical application within the PGP (see BOX 2 for additional information about the PGP).

The origins of the PGP. The research group that prepared the 2003 National Institutes of Health Center for Excellence in Genome Science proposal for a Molecular and Genomic Imaging Center to the National Human Genome Research Institute (NHGRI), a proposal that aimed to develop ultra-low cost and high-accuracy genomics[53], recognized the inadequacy of existing consent practices in the face of the increasing availability of large data sets containing comprehensive identifying genetic information. Therefore, alongside the technology change, a similarly innovative approach was implemented to obtain fully consented comprehensive genetic data sets: the PGP's open-consent protocol (summarized in BOX 3). Transparency is the hallmark of this project, which uses open-source technology and bioinformatics, relies on interactive participation by research subjects and provides open access to data sets that have been consented accordingly.

Open consent. Open consent means that volunteers consent to unrestricted re-disclosure of data originating from a confidential relationship, namely their health records, and to unrestricted disclosure of information that emerges from any future research on their genotype–phenotype data set, the information content of which cannot be predicted. No promises of anonymity, privacy or confidentiality are made. The leading moral principle is veracity — telling the truth — which should precede autonomy. Although, in clinical medicine, veracity is the legal norm in many jurisdictions, physicians may try to justify the withholding of information by invoking the 'therapeutic privilege'. In research, there is no such privilege, and when seeking informed consent from research subjects, distorted or incomplete information could undermine trust in researchers and in science.

Consenting to disclosure. Whether fully informed consent is just an ideal that cannot have a meaningful place in the practical world[51] and substantially autonomous consent is the best that is attainable is a matter of debate in ethical theory. In the PGP we strive to ensure that the consent process is as fully informed as possible, and results in a substantially autonomous consent. Therefore, the participants of the first 2007 study cohort were requested by the Harvard Medical School (HMS) Institutional Review Board (IRB) to have a master's degree in genetics or equivalent, and have been presented from the outset with a straightforward description of the risks of participation and the harm they might experience as a consequence of the loss of privacy through public disclosure or identification.

Glossary

Genetic exceptionalism
The view that being genetic makes information, traits and properties qualitatively different and deserving of exceptional consideration.

Non-distributive generalization
Generalizations that entail information about individuals as belonging to a particular group with specific properties. Any particular individual, however, may or may not have these properties.

Dictionary attack
A technique for breaking a security system by trying to determine a decryption key or a password by searching a large number of possibilities.

***L*-diversity**
A new method for the protection of privacy against adversaries with background knowledge, which requires that the distribution of a sensitive attribute in each equivalence class has the least well-represented values.

Open-source technology
A technology that is publicly available, freely distributed by the developer community and that is for the user community to modify and improve.

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The envisaged upscaling of the PGP will be guided by the outcomes of the careful monitoring of this initial cohort and by the evaluation of the participants' experiences through their continuous interaction with the project team. Interactive online education and an entrance test will be in place in order to obtain valid consent once the participation is open to the broader public.

The genetic and medical information that is posted on the study website, although it is directly associated only with the research subjects themselves, could also have relevance to participants' family members. Individuals could be traced and identified by any DNA-containing sample from their relatives who might not even be aware of its storage and its possible implications[54]. Although no consent from family members is required by the HMS IRB, in the PGP potential volunteers are strongly advised to discuss their participation with relatives.

Volunteers can withdraw from participation at any time and they can redact specific items in their records at any point in the study. They should be well aware of the fact that items that have been available in the public domain and used, for example, to support conclusions in published work cannot be easily reversed (BOX 3).

It is not promised that participation in the study will benefit the volunteers in any material way. Although individual reasons for participation may remain to a certain extent obscure, and consent might not always be based on purely rational considerations, a high degree of 'information altruism'[55] is required, thereby introducing a strong moral motive.

Concluding remarks

Current developments in genomic technology challenge the traditional normative framework for biomedical research and its well-known components. It has become clear that the common interpretation of the concepts of privacy and confidentiality as being absolute or near absolute cannot be sustained. Whenever genetic samples are involved re-identification will be possible. Although the research community is well aware of the facts, until now this awareness has not been reflected in the language of consent. Therefore, in many cases, existing consent cannot be assumed to be fully valid.

GWAS are rapidly being implemented. The first results of the NCBI Database of Genotype and Phenotype are available and are in part publicly accessible[56]. Many more studies that make use of comprehensive genotype–phenotype data are underway, and data sharing in the context of large networks is an essential part of the research process. In many cases, extant samples and data are being used in a different context and on different conditions from the ones under which they had been collected[57]. This raises serious questions about current consent practices. The burden of proof concerning ethical integrity in the conduct of research with human subjects rests with the researchers. Oversight by ethics committees or IRB approval is no substitute for personal responsibility. An open-minded reappraisal of the relationship between scientists and their research subjects is urgently needed.

New prospective studies provide the opportunity for applying newly devised consent protocols. Here, we have presented the novel open-consent model that has been devised for the PGP — it opts for openness in its scientific design and for veracity as the leading principle in obtaining participant consent.

Alternative solutions are scarce. Veracity requires broad consent in any case of collection and long-term storage of comprehensive data sets. However, an overly broad consent could become meaningless. The most likely pragmatic solution would entail maximizing data protection while informing people about its limits. Proposed solutions to the question of actual ownership of donated data and samples and of intellectual property do not bear upon the issue of promises of anonymity and confidentiality. However, taking into account the trend towards open access, the issues of ownership and benefit sharing will soon call for practical and up-to-date solutions[57].

Regulation of biomedical research will need to be revised, both at the national and the global level. We believe that sustainable solutions will only be reached through the co-development of the sciences and humanities. The role of ethics is neither that of an alibi nor of a straightjacket.

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Competing interests statement
The authors declare competing financial interests: see web version for details.

FURTHER INFORMATION
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American Society of Human Genetics: http://www.ashg.org/pages/statement_nov3006.shtml
Encyclopedia of DNA Elements (ENCODE) project: http://www.genome.gov/10005107
Genetic Information Nondiscrimination Act: http://www.genome.gov/24519851
International HapMap Project: http://www.hapmap.org
Research Program on Genes, Environment and Health (RPGEH) at Kaiser Permanente: http://www.dor.kaiser.org/studies/rpgeh/index.html
Mission statement of the Personal Genome Project: http://www.personalgenomes.org/mission.html
NCBI Database of Genotype and Phenotype: http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap
The Personal Genome Project (PGP): http://www.personalgenomes.org
UK Biobank: http://www.ukbiobank.ac.uk

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6.

Current challenges for consent: pharmacogenomics, data sharing and the language of consent

Gurwitz D, Lunshof JE, Altman RB. A Call for the Creation of Personalized Medicine Databases. Nature Reviews. Drug Discovery 5: 23-26 (2006)

Jeantine E. Lunshof. Pharmacogenetics, data sharing, and biobanking: the scope and limits of consent. A working paper for discussion.
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6.1

Data sharing

PERSPECTIVES

OPINION

A call for the creation of personalized medicine databases

David Gurwitz, Jeantine E. Lunshof and Russ B. Altman

Abstract | The success of the Human Genome Project raised expectations that the knowledge gained would lead to improved insight into human health and disease, identification of new drug targets and, eventually, a breakthrough in healthcare management. However, the realization of these expectations has been hampered by the lack of essential data on genotype–drug-response phenotype associations. We therefore propose a follow-up to the Human Genome Project: forming global consortia devoted to archiving and analysing group and individual patient data on associations between genotypes and drug-response phenotypes. Here, we discuss the rationale for such personalized medicine databases, and the key practical and ethical issues that need to be addressed in their establishment.

There is an intricate interplay between hereditary, nutritional, environmental and lifestyle factors that affect the risk, severity and age of onset of complex disorders[1,2]. Better insight into the genetic and epigenetic factors affecting complex disorders would greatly facilitate the implementation of personalized medicine that emphasizes the clinical use of individualized, genotype-based pharmacotherapy. Individual response to pharmacotherapy is determined by pharmacokinetic and pharmacodynamic factors that often depend on the individual's genotype[2,3]. The factors governing drug efficacy for complex disorders such as asthma, diabetes and hypertension are myriad and unlikely to be deciphered from studies in small patient cohorts with hundreds of patients. Many studies of complex disorders report very small genetic effects for some gene alleles, and only rarely a large contribution to disease prevalence and severity by a single allele.

The intricacy of complex disorders, and the task of developing pharmacotherapy based on genotyping, expression analysis and/or proteomics profiling, is more challenging than some initially expected[4]. Indeed, some researchers have claimed that "reviews on this topic [pharmacogenomics] have painted an overly optimistic picture — suggesting that the advent of individualized drug therapy used by the practicing physician is fast approaching"[5]. Others have taken the more positive view that the question is not if personalized medicine will arrive, but rather *when* it will arrive in the clinic[6]. It seems clear that the range of human genome diversity, combined with multiple non-heritable factors, creates a need for very large patient cohorts associated with high-quality data sets. Although improving drug safety using data from drug-metabolizing enzymes and transporter studies might be within reach, implementing drug individualization for optimal drug efficacy is significantly more challenging[7].

Web-based biomedical databases

The Human Genome Project, funded by public resources and completed 2 years ahead of schedule in early 2003, was the most publicized and successful human consortium effort in biomedicine (see Further information). It has become a gauge by which future large international biomedical research projects will be measured. National science-granting authorities globally are looking for ways to follow this success, by promoting the formation of new collaborative efforts. Indeed, the recent European Commission Sixth Framework Decision (10 June 2004) entitled 'Integrating and Strengthening the European Research Area: Life Sciences, Genomics and Biotechnology for Health' (see Further information) recommends and encourages the formation of consortia for genomics and biotechnology studies. Examples of well-known existing databases relevant to the intersection of genetics and pharmacology include DrugInteractions.com (see Further information) initiated by David Flockhart (Indiana University, USA), and the Human CYP Allele Nomenclature database by Magnus Ingelman-Sundberg (Karolinska Institute, Sweden) and others (see Further information). In the current Sixth Framework Program, a Network of Excellence has been launched, the European Model for Bioinformatics and Community Education (EMBRACE), which is a joint effort to make biological databases compatible (see Further information). A report on Human Genetic Research Databases by an expert working group of the Organisation for Economic Cooperation and Development (OECD) is expected to be published by the end of 2005 (see Further information). The recently established P3G Observatory (see Further information) is a web-based central repository for research tools facilitating the cooperation between biobanks and other population projects in genomics.

Developing web-based data resources might be the best way to stimulate the creation of a publicly accessible dataset for pharmacogenetics-based molecular medicine. The genomics era has illustrated the value of public sharing of data with the success of the National Center for Biotechnology Information (NCBI) at the National Institutes of Health (NIH), the Ensembl data resources at the European Bioinformatics Institute and many other resources worldwide. One particularly relevant precedent is the Pharmacogenomics and Pharmacogenetics Knowledge Base (PharmGKB; see Further information), which curates information relevant to pharmacogenomics, including genotypic variation, variation in drug-response phenotypes, drug-related metabolic pathways and curated literature[8,9]. PharmGKB has a world-wide mission, but the majority of data

Box 1 | **Key advantages of databases archiving PGx data from clinical trials**

Advantages for the community

- Archiving data from clinical trials in open databases would make large datasets available for academic research
- Better insight about pharmacogenetics (PGx) would allow safer and more effective pharmacotherapy for complex disorders
- Collection of PGx data from many thousands of individuals, needed for understanding complex disorders, is beyond the capacity of public efforts, and would be facilitated by archiving data from clinical trials
- Improved knowledge on genetic risk factors for complex disorders would be constructive for early detection and treatment, which is crucial for age-related chronic disorders whose prevalence is rising due to 'graying' of industrialized nations
- Open data sharing combined with innovative bioinformatics tools would increase the power and reduce public spending for scientific research
- Data sharing from negative studies (also from academia) is of considerable benefit to the community, as knowledge is gained and human as well as financial investments in redundant studies can be avoided
- Data sharing would lead to emerging standards for measuring and exchanging common drug-response phenotypes

Advantages for the pharmaceutical industry

- Identification of better drug targets owing to improved knowledge from scientific studies
- More successful drug development process on genetically targeted patient populations
- Better public image: urgently needed in light of recent public outcry over poor drug safety and increasing drug prices
- Optional advantages from commercial and regulatory incentives would result in better revenues and less risk-taking in the drug development process
- Increased information on genetic factors related to adverse drug reactions would facilitate Phase IV post-marketing surveillance, contribute to drug safety, and reduce the risk of withdrawal from the market

submissions currently come from a relatively small set of investigators who are part of the NIH Pharmacogenetics Research Network (see Further information). Although current data archived by the PharmGKB includes drug-response phenotypes linked to some individual genotypes, the number of such linked observations is still rather small. Much of the data is on genotypic variation (not accompanied by clinical phenotypic data) for polymorphic gene alleles known to affect drug pharmacokinetics or pharmacodynamics. Ideally, datasets obtained from completed clinical trials should be archived in similar open-access databases. Archiving large sets of pharmacogenetic data collected and available at the level of individual patients will allow the use of web-based data searches and powerful computational tools. Unfortunately, efforts of the PharmGKB to include datasets from completed trials have so far been futile, reflecting the lack of motivation on the part of the pharmaceutical industry to contribute such data following the completion (or cancellation) of clinical trials.

A more specialized effort to encourage pharmacogenetic data sharing is the UCSF Pharmacogenetics of Membrane Transporters (PMT) Project (see Further information), which currently curates specialized datasets about human membrane transporters. Notably, this database includes dedicated software for sharing pharmacogenetic datasets among research groups[10].

The need for data sharing

A global consortium dedicated to data sharing in pharmacogenomics would facilitate the development of individual genotype-adjusted pharmacotherapy. In particular, there should be more active sharing of individual datasets of genotype and the corresponding drug-response phenotype data after publication of scientific manuscripts — a step that seems consistent with the current tendency towards transparency and harmonization in other fields as well[11]. Presently, published manuscripts about pharmacogenetics might contain useful group data on genotype–drug-response phenotype correlates, but there is no means for sharing the individual datasets with other research groups, so that further analysis would become possible. There is, additionally, an unmet need for data sharing from unpublished studies, including unsuccessful clinical trials, cancelled trials and other studies that do not find their way into the main body of scientific literature. Unless gathered in reliable and accessible public databases, such data typically remain the property of the pharmaceutical company that ran the trial, and contribute little to the research community. Moreover, the loss of this information constitutes a breach of the trust of the patients who contributed to the research through their consent for participation in clinical trials. The basic principles of modern research ethics, including those of reciprocity and universality, generate moral obligations between groups of people[12]. Collecting samples and data for research from *individuals* gives rise to a duty for scientists to make the information available for the *collective benefit* of humankind. According to the principle of reciprocity, there is no contradiction here. The debate on data sharing has resurfaced, particularly in the European Union, in reaction to allegations that GlaxoSmithKline (GSK) was late to inform authorities of the danger of using paroxetine (Paxil) for adolescents[11]. The withdrawal of rofecoxib (Vioxx; Merck) has similarly raised public concerns about the lack of data sharing by the pharmaceutical industry[13]. Among scientists, there is an increased interest in the urgent and yet unmet need for open-access, global, continuously updated and reliable databases dedicated to records of adverse drug reactions[13].

One small but significant step in the direction of greater data sharing is the 2004 statement by the International Committee of Medical Journal Editors (ICMJE) calling for the establishment of a central registry of clinical trials[14]. This statement focused on the need to avoid bias in the publishing of data from negative or inconclusive clinical trials, as such bias significantly slows the development of medicine. A similar decision could be made by editors of leading biomedical and pharmacological journals, with regard to pharmacogenomics data from clinical trials. For example, it might be effective simply to require that data for clinical pharmacogenomics studies be deposited in a public database. An infrastructure is emerging to support the registration and tracking of clinical trials. Notable examples include the NIH Clinical Trials database ClinicalTrials.gov (see Further information) and the GSK Clinical Trial Register (see Further information). These elements, along with the large number of public genomic databases for genetic sequence data, microarray expression data, proteomics and 'boutique' gene family databases, provide a key step in disseminating knowledge about clinical studies from their inception through to the publication and submission

of datasets. The increased focus on phenotype in model organism databases, such as the Mouse Genome Informatics (MGI; see Further information), and at databases such as the PharmGKB, is the logical next step.

Ethical considerations

Ethical as well as legal considerations will play a major part in the creation of large databases for personalized medicine[15]. Researchers and the public have already begun to raise concerns about the ethical aspects underlying personalized medicine and patient privacy[16], and these concerns, in particular about data collection and individual consent, could derail the realization of personalized medicine if not addressed carefully. There has been considerable concern about an apparent conflict between the pursuit of collective versus individual interests, in particular in the context of what among the general public is known as biobanking. However, the large-scale collection of genetic data is not in itself irreconcilable with individual benefit, as, for example, rare adverse effects will only become visible from very large datasets. Therefore, this type of data collection seems fully acceptable also from the classical bioethics perspective[17]. Moreover, new ethical frameworks increasingly take into account the developments in the area of science. Recent studies in bioethics focus on, for example, the concept of genetic equity[18], and on the emerging shift in emphasis towards a community-oriented research ethics[12] without replacing individual human dignity as a core value. But it should be recognized that no ready-made, general solutions are available for the most burning issues, such as the consent for future, as yet undefined, use of data and samples, and the implications of anonymization.

Routes for moving forward

The development of frameworks for data sharing is not without major obstacles that require innovative solutions. Much information is commercial and an appropriate balance must be sought to ensure that competition and innovation are not stymied by public efforts to archive drug trials data. On the contrary, incentives should be devised so that sharing of data is encouraged and rewarded. There are several mechanisms that could be considered for promoting the willingness of the private sector to deposit data from completed (or aborted) clinical trials. In the real-world, for-profit setting of pharmaceutical companies, such incentives must be based on economic rather than altruistic concerns. The incentives could include, for example, tax exemptions for costs of collecting the genomics and proteomics data that are later deposited in public databases. A second route might include incentives of speeding up the drug application evaluation process when the relevant clinical and genomic datasets are deposited in a dedicated public database, along with a mechanism ensuring that data remain outside the public domain prior to the final drug approval. A third route for incentives could include legislation favouring lengthened patent lives for drugs whose entire clinical trials datasets are deposited in such public databases. The latter route would certainly require a major revision in the drug-application process and international patent legislation. In light of the apparent need for a major reorganization of the drug development process at large, the time seems ripe to explore such incentives with a lively public debate[19–21].

A public consortium for personalized medicine will require community supervision, administration and funding to ensure the highest data quality. Based on the experience of the PharmGKB, we can estimate that an initial investment in the range of US$50–100 million over a period of 5–10 years would potentially allow the project to begin. Larger investments might be required if the databases become successful and accumulate datasets from a large number of clinical trials.

> “The time has come to gather the accumulated pharmacogenetic data, knowledge and expertise for the benefit of the community.”

The need for reciprocity between the pharmaceutical business and the community has been an intensely debated issue[22,23]. Discussion has traditionally focused on the incapacity of developing countries to afford costs of new drugs. However, given the escalating costs of pharmacotherapy for national health budgets in industrialized nations, the issue of benefit sharing now seems a global concern. So, in the context of improving drug safety and efficacy with pharmacogenomics knowledge, having a lead role in setting-up and funding personalized medicine consortia could be an appropriate way for the pharmaceutical industry to reflect the need for reciprocity. Such support could be envisaged along the lines of the model of the SNP Consortium, which enjoyed support from the private sector for cataloguing human SNPs in a public database (see Further information). However, it is likely that public funding would also be required, and we call upon policymakers to consider the long-term benefits for society from such investments. This is one of the issues currently being studied by the Pharmacogenetics Working Group of the OECD. Notably, costs for establishing and running open ‘personalized medicine’ databases are likely to represent a small fraction of the US$3 billion of public funds put into the Human Genome Project. It would be regrettable if the improvements in human health promised by this project were not realized because of a failure to implement appropriate pharmacogenomic data-collection schemes.

The investment could pay off for society within about 20 years — in reduced healthcare costs due, in part, to a reduction in the frequency of adverse drug reactions (ADRs). In the United States alone, ADRs are estimated to cost society ~US$10 billion annually[24] and total US annual health expenditures related to lack of drug efficacy have been estimated at the staggering figure of US$170 billion[25], which is larger than the total amount spent on prescription drugs in the United States. Moreover, ADRs were estimated to account for the equally staggering figure of about 6.5% of new hospital admissions[26,27]. In addition to ADRs, pharmacogenomics also attempts to improve the efficacy of pharmacotherapy, further contributing to a potential reduction of healthcare costs worldwide.

Pharmacogenomic information collected in clinical trials and deposited in personalized medicine databases should be organized using standardized terminologies and phenotype descriptors. The complex task of accurately recording phenotypes will require

Box 2 | **Data sharing: ethical considerations**

- Reciprocity, universality and solidarity call for data sharing: individual donations to research (through trial participation) should be available for the benefit of all
- Ownership of genomic information: individual property or common heritage?
- Public trust builds on transparency: publication of any available study outcome is a moral and social requirement
- The price of the quid pro quo: reciprocity, how much is it worth?
- Effectuating data sharing — what means are needed and what can be justified: coercion, incentives, or the appeal to moral duties and social responsibility?

the use (and extension) of terminology systems such as the Unified Medical Language System[28] and its contributing vocabularies. This could include the HL7 Clinical Document Architecture, Release 2 (REF. 29), the SNOMED system for describing symptoms and diseases[30], the LOINC system for transferring information about laboratory tests[31], and improved systems for accurately classifying and describing drug-response phenotypes, such as those adopted by the Mouse Genome Initiatives[32]. The significance of creating a robust infrastructure for classifying and describing phenotypes is that it would maximize the opportunity to integrate data from different trials, standardize the collection (and exchange) of commonly measured phenotypes, and allow search and analysis of related drug-response phenotypes over the complete range of datasets brought together as part of an effort to standardize diagnostic criteria and methods for describing clinical outcomes.

The creation and continuous updating of the proposed databases would hopefully be possible with direct participation of the private sector along with publicly funded efforts[33]. Some key issues concerning the setting up of open personalized medicine databases and related ethical questions are summarized in BOXES 1,2.

Conclusions: turning data into insights

Web-based bioinformatics tools have become powerful resources for genomics studies. The power of such tools is most notable when very large datasets need to be collaboratively analysed to find subtle genotype–phenotype associations encountered in the study of complex disorders. This potential, the information from the completed Human Genome Project, and the valuable pharmacogenetic datasets collected during clinical trials must be harnessed to implement the vision of personalized medicine in the form of genotype-based pharmacotherapy. We fully agree with the statement by van Ommen that "well-accessible resources are a prerequisite for turning data into insights"[34], and open data sharing is the best instrument for building such resources.

Pharmacogenetics is not a new discipline: it is almost 50 years old, and the time has come to gather the accumulated pharmacogenetic data, knowledge and expertise for the benefit of the community. This endeavour will primarily require the collaboration of the pharmaceutical industry, which might require appropriate regulatory and financial incentives. It would also require generous public funding, as well as innovative international agreements favouring sharing and publishing of pharmacogenetic data by both the public and the private sector. The investment is likely to pay off with safer and more effective medicines, allowing reduced human suffering, smaller overall healthcare costs and improved community health. An infrastructure to support personalized medicine could be the best pay-off for the public investment in the Human Genome Project.

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Competing interests statement

The authors declare no competing financial interests.

FURTHER INFORMATION

Human Genome Project: http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml
ClinicalTrials.gov: http://www.clinicaltrials.gov
DrugInteractions.com: http://www.drug-interactions.com
EMBRACE Network Of Excellence: http://www.embracegrid.info
European Commission Sixth Framework Decision: Integrating and Strengthening the European Research Area: Life Sciences, Genomics and Biotechnology for Health: http://www.mrc.ac.uk/pdf-WorkProgTP1-call3.pdf
GlaxoSmithKline Clinical Trial Register: http://ctr.gsk.co.uk/welcome.asp
Human Cytochrome P450 Allele Nomenclature Committee: http://www.imm.ki.se/CYPalleles/
Mouse Genome Informatics: http://www.informatics.jax.org
NIH Pharmacogenetics Research Network: http://www.nigms.nih.gov/pharmacogenetics
Organisation for Economic Co-operation and Development: http://www.oecd.org
P3G Observatory: http://wwwp3gobservatory.org
PharmaGKB: http://www.pharmgkb.org
The SNP Consortium: http://snp.cshl.org/
UCSF Pharmacogenetics of Membrane Transporters: http://pharmacogenetics.ucsf.edu/
Access to this interactive links box is free online.

6.2

The language of consent

Pharmacogenetics, data sharing, and biobanking: the scope and limits of consent

Points to consider for model consent language – a working paper for discussion

Jeantine E Lunshof
in cooperation with Russ B Altman & David Gurwitz Version June 2008

Task #4 of the Pharmacogenetics Research Network Data Sharing Action Group, as decided at the Group's meeting, 17 November 2006, Cold Spring Harbor Laboratory, and confirmed 1 December 2006, included the following deliverables:

• Review, and compare the proposed PGRN Recommendations for Model Informed Consent Language, Terms, and Procedures (Oct. 2006, Julie Johnson) with other relevant consent documents;

• Defining criteria for relevance of consent models & selecting consent models appropriate for comparison;

• Generate recommendations and report on possible refinement or expansion of the October 2006 document.

1. Inventory & first analysis

In the first phase of Data Sharing Action Plan Task 4 an inventory has been made of projects and consents that could be of potential interest. Preliminary findings were presented April 2007. The analysis included consent documents from the following projects:

1. The Pharmacogenetics Research Network - PGRN
2. The database of Genotype and Phenotype - dbGaP
3. The Genetic Association Information Network – GAIN
4. The Marshfield Clinic Personalized Medicine Research Project
5. The Kaiser Permanente Research Program on Genes, Environment and Health - RPGEH
6. UK Biobank
7. The DatabasE of Chromosomal Imbalance and Phenotype in Humans using Ensemble Resources – DECIPHER
8. The Personal Genome Project – PGP

9. The International HapMap Project

Special cases:

10. Erasmus Rucphen Familieonderzoek – ERF
11. The Icelandic Health Sector Database – IHD

Only a small number of projects have been considered, the main criteria for inclusion being:
• focus on combined genotype-phenotype information,
• focus on PGx or development of personalized medicine,
• the availability/accessibility of project information.

Also 'visibility' of projects was taken into account, as some projects serve as paradigm cases in the literature and beyond that in the public perception (IHD) while other projects are less visible or even intentionally hidden (ERF). Also some examples have been included that show the – current – ethical and social limits of GWAS research. Table 1 provides an overview of the main features of the projects and key 'parameters' of the consents.[1] Detailed information on these projects can be found in Appendix I.[2]

Legends Table 1:

#1 The Pharmacogenetics Research Network - PGRN
#2 The database of Genotype and Phenotype - dbGaP
#3 The Genetic Association Information Network – GAIN
#4 The Marshfield Clinic Personalized Medicine Research Project
#5 The Kaiser Permanente Research Program on Genes, Environment and Health - RPGEH
#6 UK Biobank
#7 The DatabasE of Chromosomal Imbalance and Phenotype in Humans using Ensemble Resources – DECIPHER
#8 The Personal Genome Project – PGP
#9 The International HapMap Project

[1] In Table 1, the type of coding is classified according to the recently adopted ICH terminology (coming into operation May 2008): ICH, *E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories*. http://www.ich.org/LOB/media/MEDIA3383.pdf
[2] The appendix is not attached to this version.

PROJECT	**#1** PharmGKB	**#2** dbGaP	**#3** GAIN	**#4** PMRP	**#5** RPGEH	**#6** UK Bb	**#7** DECIPHER	**#8** PGP	**#9** HapMap
type of project/collection:									
stand-alone (single contributor or closed network) or open network (many contributors)	open	open	open	stand-alone	stand-alone	stand-alone	open	stand-alone	stand-alone
sample/data source									
new inclusion dataset	No	No	No	Yes	Yes	Yes	No	Yes	Yes
new samples	No	No	No	Yes	Yes	Yes	No	Yes	Yes
extant: data/sample for research purposes or for clinical purposes	Both	Both	Both	Clinical	Clinical	Clinical	Both		
consent:									
new & specific **or** existing	Existing	Existing	Existing	new & specific	new & specific	new & specific	new & specific	new & specific	new & specific
type	unknown	unknown	unknown	multiplex	blanket Use without consent possible	blanket	multiplex	open	blanket
coding:									
ICH Terminology	coded s/d	coded s/d	coded s/d	coded s/d	coded s/d	coded s/d	coded s/d	identified	anonymized
what is being stored / curated:									
genotype									
samples (repository)/ data (database) / both	Data	Both	Both	Both	Both	Both	Both	Both	Both
phenotype									
minimum (gender, age, ancestry) or comprehensive (medical record, lifestyle, environment)	Comprehensive	Compre hensive	Comprehensive	Comprehensive	Comprehensive	Comprehensive	Comprehensive	Comprehensive	Minimum

Table 1

Some interim conclusions:
• the proposed PGRN template for consent for PGx-related studies seems very useful.
• only a limited number of other consent forms needs to be taken into consideration for further evaluation of usefulness.
• notably the Marshfield Clinic Personalized Medicine Project information + consent material deserves careful consideration.
• the scientific and the governance structures of large network and consortium efforts (notably dbGaP, GAIN) determine the framework within which – in the end - the consent should apply. At the same time, both the design, the approval, and the implementation of the consent (content and procedures) are the responsibility of the local institutions, clinical and research practice.

This latter point turns out to be the pivotal issue: the discrepancy between the circumstances for which the consent has been designed and initially applied, and the further context in which it finally will be used of large-scale genomics research, with data sharing as a main feature.
This point applies both to pharmacogenetics and other studies.

SACGHS Report on PGx
Realizing the Promise of Pharmacogenomics: Opportunities and Challenges
http://www4.od.nih.gov/oba/sacghs/reports/SACGHS_PGx_report.pdf

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) published on 12 May 2008 a report on pharmacogenomics:
Realizing the Promise of Pharmacogenomics: Opportunities and Challenges
Notably, the SACGHS committee mentions consent among the items that "may affect the willingness of patients, clinicians, and health care managers to participate in PGx research and apply this information in clinical practice".(p. 39)

The report chapter on Informed Consent (p. 42-43) includes a detailed explanation on the discrepancies between HHS regulations, in which research using anonymized samples is not considered to be human subjects research (and therefore not requiring consent) and the FDA regulations which always require informed consent.
The chapter concludes with the statement that "broad consent may lead to uninformed decisions, whereas narrow consent can hinder research. Additional guidance may be needed to help investigators design consent processes that maximize the benefits of research while preserving adequate levels of choice."

Some further insights related to informed consent are discussed on the chapter on "Health Care Providers" (p. 71-73). The report gives the example of PGx tests whose results also pertain to cancer risks: "PGx tests may reveal unrelated or unanticipated information in addition to the test result originally sought. For example, some drug-metabolizing enzymes identified by PGx diagnostics also interact with environmental toxins; consequently, test results might reveal susceptibility to certain cancers. The psychological effects of such a

revelation can be considerable. As such, health care providers offering diagnostic testing with the potential to reveal damaging secondary information are advised to ensure that the test is performed at a certified laboratory to ensure test accuracy. They also are advised to counsel patients about the possible risks and benefits of PGx testing or refer them to a trained genetic counseling provider."
Matters pertaining to informed consent are further discussed in the ELSI section of the SACGHS report (p.148-151)

2. Key issues in consent to pharmacogenetics research participation

In this section the following topics will be addressed that are relevant for consent to participation in pharmacogenetics studies

1) Are pharmacogenetics studies different from other biomedical research, do they require specific consent?
2) Multilayered studies, the implications for consent
3) *de novo* studies and research on extant data & samples

2.1 Consent for studies involving PGx - a special case?

Should there be specific consent for pharmacogenetics studies, as a primary study or as an add-on, in clinical trials or other biomedical research?
Researchers involved with study design, as well as institutional review boards involved with the approval of study protocols, increasingly face the question whether there are specific features to pharmacogenetics and pharmacogenomics research that should be reflected in the study consent.
In a recent article on a comparative study of consent, Phillips et al. raises a number of ethical challenges for informed consent in pharmacogenomics.[3] They identify five key issues: scope of consent, duration of consent, confidentiality and coding of samples, return of research results, and separate consent for 'add-on' pharmacogenomics studies. However, not all of these issues are specifically relevant to pharmacogenomics or pharmacogenetics studies, as they are equally important for any other study consent.

What are the specific issues in consent for pharmacogenetics research?
At least the following specific and interrelated features of pharmacogenetics research need to be taken into account when designing consent for study participation:

[3] Phillips MS, Joly Y, Silverstein T, Avard D. Consent in pharmacogenomic research. GenEdit (2007) 5(2):1-9. Available from http://www.humgen.umontreal.ca/genedit .

1) The need for pharmacogenetic genotyping – in studies that are otherwise not using any genome data.

2) The possibility of ancillary information being generated by pharmacogenetic findings. This may result from the genotyping or from the study outcomes. The impact of such findings might be either direct – e.g. conveying prognostic information about the disease that is being studied –, or it may consist of highly probabilistic information on susceptibility for disease.[4]

3) The fact that results may be of immediate relevance to research subjects; e.g. information on CYP polymorphisms, like CYP2D6 metabolizer type, that can have direct impact on drug prescribing and may lead to a reduction of harm through adverse drug reactions.

4) The return of study results. Both the aspects of ancillary information (2), and directly beneficial information (3), are of immediate relevance for deciding about the strategy regarding the return of study results. This is not a trivial issue. Study participants may or may not want to be informed about ancillary information; at the same time, withholding directly beneficial information will be hardly justifiable. For example, results of tests on CYP polymorphism taken as part of PGx-related clinical studies e.g. for decisions on drug prescription may impact on the individual cancer risk, as noted by the SACGHS report. Certain alleles for CYP and other drug metabolizing enzymes have been described as strong endometrial cancer risk alleles, some having high odds-risk (OR) factors of above 4, that is, not at all negligible[5]. Should the consent forms for PGx tests therefore warn the participating individuals that they may be exposed to information on their cancer risks, which may cause them undue stress, while not being related to their current treatment and study aims?

5) The method of coding samples and information. If there are good arguments for returning pharmacogenetics research findings to participants, as suggested under (4), then, enabling this option will be a major factor in deciding upon the coding strategy for data and samples. Although usually other factors will be decisive with regard to the coding strategy for data and samples in research, the option of returning study results to participants requires the research subjects being re-identifiable. Reluctance concerning the feedback of individual study results to participants is the default mode of current research practice.[6] It is questionable whether this routine can be justified in pharmacogenetics research.

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[4] A comprehensive analysis including recommendations on incidental findings (IFs) has been published in June 2008. It addresses IFs in research, not in clinical care. Genetic family studies and research using genomic microarray s are among the examples in this publication, PGx testing is not explicitly addressed.
Wolf SM, Lawrence FP, Nelson CA, Kahn JP, et al. . Managing Incidental Findings in Human Subjects Research:Analysis and Recommendations. Journal of Law, Medicine & Ethics, (2008) Summer 2008 (preview from authors)

[5] Hirata H, Hinoda Y, Okayama N, Suehiro Y, Kawamoto K, Kikuno N, Rabban JT, Chen LM, Dahiya R. CYP1A1, SULT1A1, and SULT1E1 polymorphisms are risk factors for endometrial cancer susceptibility. Cancer. 2008;112(9):1964-1973.

[6] Renegar G, Webster CJ, Stuerzebecher S, Harty L, Ide SE, Balkite B, Rogalski-Salter TA, Cohen N, Spear BS, Barnes DM, Brazell C. Returning Genetic Research Results to Individuals: Points-to-Consider. Bioethics 2006;20:24-36

6) The issue of privacy versus re-contacting & re-consent. Promising feedback concerning individual research outcomes, necessarily implies refraining from promising strict privacy, anonymity and confidentiality.[7] The trade-off between the beneficial impact of returning research results and the assumed detrimental – social - effects of giving up 'anonymity' may vary in different social and research contexts. A case-specific consent may seem appropriate. This, however, will turn out to be a short-term solution only, as data-sharing and future further use of data and samples would require re-contacting and re-consent unless this is radically precluded by initial narrow consent. See below under paragraph 2.2.
In particular in pharmacogenetics research, the interests of the study participants may be served best through open, interactive researcher-participant communication.

2.2 The scope of consent: broad, narrow, blanket, or multiplex?

The scope of consent pertains – apart from consent to interventions and procedures - to both the direct purpose and use of study results and to the future further use of samples, data, and study outcomes. Data sharing is a key issue that adds to the scope and duration of consent, the dimensions of time, place and 'unknown' users. Narrow, broad, or blanket consent are the commonly applied notions. However, study protocols can be extremely complex and will often require an accordingly 'multiplex' consent.

Protocols can consist of the following elements in case of a main study that itself can be a PGt/PGx study or not (this paragraph only looks at the scope of consent; coding / return of results issues are not included):

Types of consent: basic criteria					
	Type	Data sharing	Data storage / biobanking	Future use	Type of consent
Features of study	a	no	no	no	narrow consent
	b	yes	yes	restricted: original purposes	broad consent
	c	yes	yes	unrestricted	blanket consent

Table 2

a) Main study: no data sharing; no long-term data storage / no future use. [8]
→ narrow consent
b) Main study: data sharing; submission of data/samples to biobank; future use; use restricted to scope of original purposes.
→ broad consent

[7] Lunshof JE, Chadwick R, Vorhaus DB, Church GM. From genetic privacy to open consent. Nat Rev Genet (2008);9:406-411
[8] one place, one-time use – it is the question whether this in itself is ethically justifiable research.

c) Main study: data sharing; submission of data/samples to biobank; future use; unrestricted further use.
→ blanket consent

In the case of a combined main study with a PGt/PGx study as an add-on all combinations of consent are possible, from:
aa) Main study: no data sharing; no long-term data storage / no future use
→ narrow consent
Add-on: no data sharing; no long-term data storage / no future use
→ narrow consent
To:
cc) Main study: data sharing; submission of data/samples to biobank; future use; unrestricted further use.
→ blanket consent
Add-on: data sharing; submission of data/samples to biobank; future use; unrestricted further use.
→ blanket consent

The bottom line is, that narrow consent is only appropriate if no data sharing, no storage, and no future use will take place. This will hardly ever be the case.
As soon as unrestricted future use is intended (or: not excluded) blanket consent is appropriate.
In any other case broad consent may apply, however, as scientific developments cannot be foreseen, there is a considerable risk that the broad consent that was obtained initially will no longer be adequate or can no longer be complied with.

Multiplex consent will be necessary for many studies that include additional PGt/PGx protocols. This makes high demands upon researchers with regard to the design of the study protocol and of the participant information on which consent will be based. At the same time it also poses a big challenge to review boards and regulatory bodies, both at the initial approval before study begin and later, in situations where approval for further use of then extant data and samples is being sought.

2.3 De novo studies & extant collections

How can the discrepancies be reconciled between initial consent for study participation and further use of data in studies that differ in significant respects from the original study for which the consent was given? The further use of so-called extant data and samples raises fundamental questions concerning the limits to the validity of consent.

To a review board, assessing a *de novo* study protocol and the accompanying consent may seem a piece of cake compared to the thorny issues raised by protocols that involve the use of existing collections of data and/or samples.[9]
In many cases initial consent for research use may be lacking completely, for example when clinical specimens are concerned. **If initial consent is available, the assessment of its being applicable to the proposed further research is a matter of interpretation of the wording**. Even if this may seem theoretically clear, it may not work in practice.
With large databases and repositories, the responsibility for the quality and validity of consent of individual data or studies submitted, rests with the original researchers. The mosaic of terms and conditions of the original consents of the data sets submitted to large databases, as for example, dbGaP or PharmGKB, makes it virtually impossible to retrieve for further research data sets that have uniform 'terms of use'. The subsequent research adds a further layer of conditions to the data's terms-of-use history.

Any consideration of seeking re-consent, or the suggestion of the option of withdrawal of data and or samples, depends upon the feasibility of re-identifying, tracing and re-contacting the individual research subjects. Although DNA is an identifier in itself[10], identifying and tracing individuals by matching DNA sequence data from different sources will rather not be the way to obtain re-consent. Breaching database security systems will be neither.
This means that, when extant data and samples are at stake, any claim about respecting autonomy of research subjects is void in case of supposedly 'anonymized' data sets – a fact that is often overlooked, and 'respecting expressed wishes' or '(dis)regard sample donors' own views' presuppose identifiable research subjects. But, 'discouraging requirements for informed consent for each new study', cannot be the solution.[11]

2.4 Concluding remarks

Today, the question concerning the consent for the re-use of extant samples and data that are under the custody of biobanks urgently calls for practical and sustainable solutions.
Referring to respect for individual autonomy, in particular when applied to 'anonymized' extant data and samples, is largely rhetoric. Concerns about damage to the public trust in researchers and in science are not imaginary[12].
Currently, the sole responsibility for the quality and validity of the consent rests with the submitting researchers. The question arises, whether in case of extant data and samples the biobanks should have a more substantial role in the control of data sharing. One concrete instrument could be the development of a minimum set of criteria for scrutinizing the scope of

[9] Though, we should be aware that today we produce the extant data of tomorrow.
[10] The American Society of Human Genetics. ASHG Response to NIH on Genome-Wide Association Studies. 30 November 2006. <http://www.ashg.org/genetics/ashg/news/gwas.shtml>
[11] Helgesson G, Dillner J, Carlson J, Bartram CR, Hansson MG. Ethical framework for previously collected biobank samples. Nat Biotechnol 2007;25:973-976
[12] Childress JF, Bernheim RG. Public health ethics. Public justification and public trust. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2008;51(2):158-163.

consent – or the context from which the data originate in case of absent consent – at the moment of data submission.
In general, adding to the existing thicket of regulation does not tend to promote research efficiency.[13] However, it might be worth to consider whether the role of the biobanks as intermediates in data sharing should get some more profile. Increase of transparency should be the only aim – but one that the research community owes to the individual donors of biological samples and phenotypic data, to their communities, and to society.

[13] Lunshof JE. Desperate times call for desperate measures. Nat Rev Genet 2006;7;162

7.

Outlook on theory development and education

Lunshof JE . Teaching and practicing pharmacogenomics: a complex matter
Pharmacogenomics 7: 243-246 (2006)

OPINION

Teaching and practicing pharmacogenomics: a complex matter

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This opinion is a reply to the following article: Flordellis CS: The emergence of a new paradigm of pharmacogenomics. *Pharmacogenomics* 6(5), 515–526 (2005).
Systems biology is likely to become a leading paradigm in molecular biology in coming decades. In pharmacogenomics, complexity is rapidly increasing as more genomics and proteomics data become available. Tackling this complexity by employing a systems approach seems to be a promising strategy. The introduction of this new paradigm will reshape both professional education and clinical practice. Professionals in medicine and the life sciences must be prepared to adapt to this new approach. However, systems-based pharmacogenomics is unlikely to be ready for clinical application in near future. In order to benefit patients today, the already available options of pharmacogenomics should be carefully implemented in clinical practice as soon as possible. Teaching the current, continuously updated knowledge of pharmacogenomics should not be postponed until the new paradigm arrives.

In his insightful article in *Pharmacogenomics* on the emergence of a new paradigm of pharmacogenomics [1], Flordellis describes the shift toward systems biology, and consequently calls for *"another understanding of education in the field (of pharmacogenomics [PGx]), which aims at stimulating a critical reflection on these major shifts prior to a practical training on the immediate application of pharmacogenomics"*. He also calls for *"a distancing from the deterministic genome-centric approaches, in favor of a more integrative application of PGx"*, thereby aiming at systems biology-based pharmacogenomics.

As a philosopher and bioethicist, I can subscribe to this call that addresses crucial issues. However, in this article I would like to examine some aspects in more detail. A paradigm shift in biology toward an approach based on systems theory thinking will have a deep impact on basic research, on clinical practice and on teaching – from school curricula in biology to post-doctoral studies in medicine and the life sciences. Assuming that a shift toward systems thinking is a likely development, its accomplishment will be a huge effort, next to a scientific revolution, in terms of Thomas Kuhn's theory [2] (**Box 1**).We are now only at the very beginning of this development. Therefore, I will argue that the teaching and application of pharmacogenomics cannot wait until the new paradigm of systems biology will have reached the stage of, in Kuhn's terms, 'normal science'. Today we should implement in clinical practice our current knowledge to the best of our abilities, yet prudently, maximizing therapeutic benefit without raising false expectations. The big challenge for education is to teach our medical and health sciences students the concept of pharmacogenomics in a way that is understandable within the framework of current knowledge, but at the same time enables the students to quickly adapt to new insights that are likely to arrive in the near future.

With reference to Flordellis' arguments, this paper will elaborate on the following issues:

- Pharmacogenomics and complexity
- Systems-based education for the health professions
- Implications for current practice and future developments

Pharmacogenomics: complexity vs. application?

Flordellis rightly affirms that drug response phenotypes cannot be predicted by genotype alone, as represented through single nucleotide polymorphisms (SNPs) and haplotypes. Indeed, if this was the case, a rather widespread application and clinical implementation of PGx could have been established by now. The emerging complexity of PGx, in particular with respect to the genomics of drug efficacy, is likely to be a major reason for the delay of its translation into practice, in drug development and in clinical use in pharmacotherapy [3,4]. Tackling this complexity by way of a systems approach seems to be a promising strategy. The

Keywords: clinical application, complexity, education, endophenotype, epigenetics, ethics, paradigm shift, pharmacogenomics, systems biology, systems theory

future medicine

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Box 1. The structure of scientific revolutions.

Thomas S Kuhn, physicist and philosopher of science, published his groundbreaking work *'The structure of scientific revolutions'* first in 1962 and a revised edition in 1970. Key notions in this theory about the evolution of science are:

- Progress in science is not a linear, gradual process, but results from periodic revolutions: paradigm shifts.
- Normal science represents the dominant paradigm at a given moment in time.
- New paradigms can emerge when normal science fails in puzzle-solving and new theories emerge from the resulting crisis.
- Acceptance of the new paradigm by the majority of the scientific community marks the establishment of new normal science.
- The new paradigms of normal science after a scientific revolution are incompatible with the old paradigms. Those who stick to the old paradigms loose their scientific credibility.

systems theory offers an explanatory framework that enables us to understand complex phenomena as such – as being a result of the interaction of the parts that make up a particular system, and that give rise to properties of the system that are not reducible to the properties of the single parts [101]. Modern systems theory [5] has been influencing biology [6] at the fundamental theoretical level over several decades, however, with little practical spin-off. As shown by Westerhoff and Palsson, the sequencing of the human genome and the emergence of a data-rich biology made systems analysis critical to molecular biology [6] (**Box 2**). Currently, the impact of systems biology is rapidly increasing, particularly in the field of drug discovery [7,8], and is regarded by its proponents as a prerequisite for the successful establishment of personalized medicine [9]. However, the development of systems biology is still in its infancy and, as holds for personalized medicine itself, it remains to be seen whether it lives up to its high promises. Critics have claimed that systems biology raises unrealistic claims, and uses unclear definitions and inadequate methods [10]. In the future, regarding the development and implementation of pharmacogenomics, the systems approach might offer the clues to solving many of the problems that currently limit its clinical application. However, within these limits the implementation of currently available knowledge is already possible, to a certain extent, and should be pursued. Recommendations for genotype-adjusted prescribing of cytochrome P450 (CYP)-metabolized drugs have been available for several years [11,12] and conventional, in addition to innovative microarray-based genotyping technology, is available [13,102]. The effectiveness of this strategy, in terms of benefiting patients through the reduction of adverse drug reactions (ADRs), is awaiting empirical evidence that can only be gained from controlled clinical trials. It is implausible to expect that systems biology would be able to offer an all-inclusive solution for pharmacogenomics within the foreseeable future. Therefore, a more pragmatic approach is needed. Through a prudent implementation of our, admittedly limited, current knowledge pharmacogenomics can become part of medical care today, reducing suffering and improving quality of life [14,15].

Systems thinking in education

With regard to pharmacogenomics education, Flordellis criticizes its instrumental and procedural character. He certainly has a point here. However, I cannot share his interpretation of *"the project of education in PGx (being) tacitly transformed to a conservative package to be targeted to the practicing behavior of the new healthcare professionals"* [1]. The reality of the state of the art in systems biology and PGx on the one hand, and of the educational needs of students in the health sciences as well as of practicing professionals on the other, dictates a pragmatic and differentiated approach with regard to educational programs. From the developments so far, it seems evident that systems biology should have ample space in the biology and life sciences curriculum. The future will show whether it will replace the traditional paradigm in biology, or be merely supplemental to it. In the curricula for the health professions, systems-based approaches are, to varying degrees, being incorporated [16,17]. Notably in the theory of nursing, the systems-based or integrative approach was incorporated as early as the 1970s [18]. However, this direction in systems thinking needs to be clearly differentiated from the scientific direction of systems biology. The proof of systems theory's power for puzzle-solving in basic science differs significantly from the proof required to confirm its applicability to biopsychosocial interactions. Another caveat related to this is that systems thinking is not a moral practice, even if there may be ethical aspects to some of its applications (**Box 2**). This needs to be clear when introducing systems thinking in education. Teaching modules for PGx will need to be developed in a way that is consistent with the basic concepts of the respective curriculum. As for other subjects, the curriculum should contain continuously updated information on the current state of the art of PGx and its clinical applications, as well as on the prospects for future implementation. In this respect, it is not different from, for example, neurology or reproductive medicine. Continuing

Box 2. Systems theory and systems biology.

- Systems theory studies systems as a functioning whole, and focuses on the interaction of the components that make up a system, and its emergent properties instead of the properties of the single components.
- Emergent properties are unpredictable. Systems are irreducible to their constituent parts [101].
- Originating from the early twentieth century theory of mathematics and philosophy, modern systems theory [5] has been influencing biology at the fundamental theoretical level over several decades; however, with little practical spin-off.
- The sequencing of the human genome and the emergence of a data-rich biology made systems analysis critical to molecular biology [6].
- Systems biology is still in its infancy, but may very well be the prelude to a 'scientific revolution'.

Systems theory, 'holism' and morality

Because systems theory studies systems as a functioning whole, it is often called holistic. However, this term as such contains no information, and is controversial. Moreover, it is tainted by its use in various contexts where 'holism' is equivalent to morally 'good' and 'reductionism' to morally 'bad'. Therefore, its use should rather be avoided in a scientific context.

medical education (CME) programs for health professionals, be it for physicians, pharmacists or nurses, will usually need to focus in the first place on developments that are available for immediate implementation. These programs must take into account the conventional framework of reference of the participants to be able to deliver the teaching content.

Outlook

How should we, as clinicians and health professions' educators, deal with the emerging paradigm shift? In the short term, a two-tier strategy will be needed for a realistic approach of both the implementation of PGx and education. Incremental implementation in clinical practice of current options of PGx is the only way to collect data on its clinical utility. It will also show the level of acceptance by patients and by the healthcare profession. At the same time, carefully collected data on genotype/drug-response phenotype relationships will be indispensable for the development of clinically useful systems-based PGx. Promising future developments, for example, the use of endophenotypes [1,19], are dependent upon the availability of large sets of reliable genotype/phenotype data [20]. If the concept of endophenotypes, based on the allelic comparison between affected individuals and nonaffected first-degree relatives, finds broad use in clinical practice it will revive many of the ethical questions that were thought to have been already dealt with adequately. Questions concerning carriership of genetic traits, of predictive testing, and of disclosure of genetic information within families will be shown in a new dimension. Progress along the lines of the emerging paradigm of systems thinking will therefore necessarily be rooted in the 'deterministic genome-centric approach' [1] that has been guiding us so far. This is evident with regard to epigenetics: as the epigenotype is imposed upon the genotype, we need to know the genome to be able to interpret the epigenome [1]. The same holds true for education. Education on clinical applications today must take place within the framework of the reference of today's practitioners. In medical and health schools curricula we can make the students familiar with new basic concepts, applicable today only in research settings, but pointing toward concrete future options. Nevertheless, advancing the education of PGx to *"a platform for the thematization of a series of transitions in the understanding of multigenic systems"*, as proposed by Flordellis, is a commendable goal.

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Highlights

- A paradigm shift in biology toward systems biology is a likely development.
- The increasing complexity of pharmacogenomics (PGx) is a major reason for the delay of its translation into practice, in drug development as well as in clinical use in pharmacotherapy.
- Tackling this complexity by way of a systems approach seems a promising strategy.
- The teaching and the clinical application of pharmacogenomics cannot wait until the new paradigm of systems biology is established.
- Currently available knowledge in pharmacogenomics and pharmacogenetics, imperfect as it is, should be used for improving quality of care in pharmacotherapy today.
- Systems biology should be part of the medical and life sciences curriculum today, preparing our professionals for the future. Teaching modules for pharmacogenomics should be future oriented, but must start from current knowledge.
- Systems thinking as such has no moral qualities: it cannot be morally right or wrong.
- The application of new concepts, for example, the concept of endophenotypes, will bring new questions for ethics and also revive old ones.

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8.

General discussion

8. General Discussion

8.1 The initial questions

The initial key question was: “ethics in genomics – does it still work?”
Subsets of the key question dealt with the role of ethics in genomics, and the reverse, the influence of genomics on ethics.
I have tried to show that while ethics is still quite busy with genomics it may have reached its limits in the particular role that has been assigned to it in this context, a thorough revision of which appears to be indicated. Currently, this role of ethics is firmly established – although it suggests ethics being not much more than a governance instrument in the context of ELSI. Given the history, this is no surprise: ELSI, as a governance instrument in genomics, has been focused on bioethics from its inception in the late 1980s, addressing familiar questions of medical and research ethics and referring to established frameworks of normative ethics for drafting its policy recommendations. This way, ethics became a crucial tool for genomics’ governance.
Why has it reached its limits – and in what respects does this role need revision?
In the following I will discuss the challenges that arise from the scientific developments in genomics, the problem of governance, and also address the question of the role of ethicists as insiders or outsiders in their involvement with genomics research.
I am convinced that ethicists – building upon the vast body of knowledge of philosophy – can make substantial contributions to the theory and practice of governance. At the same time, I believe that there is a genuine role to play for ethics and philosophy through direct engagement in highly innovative research endeavors and the related theory development.

8.2 Ethics & genomic science: where are the challenges?

The challenges for ethics in its current role within the ELSI context in genomics come from several directions. First, there are the rapidly changing empirical facts resulting from the developing science that ethics needs to take into account. Second, there is the intricate relationship between the pursuit of genomics research at a global scale and its governance: genomic science develops within a context of international cooperation and competition, requiring international – global – organizational structures. These structures, in turn, impact upon the science they are governing and influence the course of the developments through a range of mechanisms – that are the subject of critical analysis for specialized branches of the social sciences. Law and ethics are called upon for the design of normative frameworks, as the backbone of governance structures, providing procedural rules as well as justifications, e.g. by framing the declared mission of the organization.

Turning to the changing empirical context – the general overview article in Chapter 1 lists four instances of relevant features of current genomics:

• *scale and pace*: e.g. the consortium efforts and the networks of networks involved with genome-wide association studies (GWAS).[1,2] The huge magnitude of the studies (typically with several thousands of participants, and a large number of participating research groups from a vast range of countries) allows outcomes to be obtained much faster and provides the statistical power needed for finding genome/phenome associations that would not otherwise be attainable. These complex mega-projects require robust governance infrastructures, that will routinely include ELSI. A typical ELSI challenge arises, as the single studies that make up the large GWAS consortia and networks like GAIN[3], contribute extant data and samples to the collective effort while such use of data was not foreseen at the moment that the research subjects entered the original study. Inadequate consent for further use of extant samples is one example of a problem that cannot be solved within existing normative frameworks; this is among the questions addressed in Chapter 5. Innovative legal concepts have been proposed[4], but so far not put into practice.
• *technology and methods*: notably, the advances in high-throughput sequencing (that can be seen as an example of increase in scale and pace too), but also in microarray technology, multiplex PCR, and bioinformatics create new options and raise new questions. High-throughput sequencing and, in particular, the development of microarray technology have contributed to the broad availability of genotyping that has facilitated – apart from a vast range of pivotal clinical applications – the direct-to-consumer marketing of genotyping services for a wide range of purposes (genealogical; nutrigenomics; pharmacogenetics; disease- and susceptibility related profiles as part of personal genomics, etc.). Chapter 3 deals with some of the possible ethical implications of 'genomics for all' in the practice of clinical medicine. The direct access to genotyping for consumers is an example of a scenario that could only become a reality through advances in technology and data processing.
• *theory development in the genomic sciences and shifting paradigms*: this includes hypothesis-free and hypothesis-generating research (GWAS), shift towards systems biology, the crucial role of bioinformatics. Hypothesis-generating research has a number of implications that are relevant to ethics. If it is applied in prospective research with *de novo* enrollment, there is a fundamental theoretical problem with substantive *informed* consent: research subjects must consent to the 'unpredictable unknown'. Actually, this may be more often the case in studies and usually remain obscure (and in such cases there should be doubts about the validity of consent), but devising adequate consent for hypothesis-generating or -free research poses major challenges to ethics and epistemology. The same holds true for the application of systems biology: likely, 'information content' (i.e. of research outcomes) will need to be redefined in a way that acknowledges the dynamics and interdependent elements of a system and procedures for adequate communication of findings to participants must be developed. Redefining concepts – including concepts of health, disease, and even 'gene'[5] – will only be possible through direct reciprocal interaction with the evolving science and the scientists. The translation into clinical practice and the integration of the paradigm shift towards a systems-based approach into education also challenges the established practices and theoretical frameworks underlying

curricula in health and life sciences. Some aspects of this uneasy change have been addressed in Chapter 6.

• *novel practices*: for example, centralized data storage, data accessibility and sharing, web data storage and increasingly powerful and user-friendly web-based search engines. Obviously, centralized data bases and sample repositories call the whole ELSI repertoire to arms. The same, however, applies to projects aiming at the integration and harmonization of decentralized or cross-border facilities, as e.g. the recent European biobanking initiative.[6] A novel practice in web-based storage and search options are the online electronic health record (EHR) projects that are offered direct-to-consumers as commercial initiatives.[7] The impact of the combination of these comprehensive data sets with the genomic data bases – comprising of clinical and research data as referred to above – cannot be predicted yet. As noted in the Introduction, the changing position of the individual, influenced by increasing direct access to actionable knowledge (and therefore, a shift towards preventative medicine)[8] makes it necessary to take new models into account: a remodeling of 'patients' or 'research subjects' into *individuals as agents* is around the corner. The direct-to-consumer offering of services – be it genomics-based or in the field of imaging technologies – that provide individuals with information that so far used to be available in the clinical setting only, creates a new form of agency which is located between that of the patient and the consumer: personal genomic information has become a commodity already. Also, large numbers of individuals become increasingly involved as volunteers in research, for example by participating in population biobanks[9] or in other large-scale epidemiology or comprehensive genomics projects.[10] This shift that is enabled by web-based forms of interaction – either for commercial purposes or for communication with researchers – allows for virtually unlimited outreach and access to knowledge and services. It will likely impact upon, for example, current concepts of autonomy and profoundly influence post-genomic ethics.

A special and highly relevant feature of these developments is that we are witnessing simultaneously very large-scale research, in particular the consortium efforts in genome-wide association studies, and very small-scale yet comprehensive research of individual whole genome sequencing in the form of 'personal genomes'. We should be aware of the fact that the process is circular: genome-wide association studies ultimately rely on data collected from individuals, while the interpretation of individual sequence and integrative genomics information is only possible through computational exercises on vast amounts of data obtained from very large cohorts of individuals. The large scale and the comprehensiveness, as well as the circular nature of this process are unprecedented and necessitate an overhauling of concepts and innovative steps in philosophy and ethics, as well as in the other ELSI related disciplines. There are many aspects to these developments that do need regulation (apart from analysis and reflection by ethics) and newly devised or existing regulation must be adapted to the new issues. For example, the DTC marketing of testing may require appropriate product liability legislation (taking into account global markets), and it may also impact on professional liability of health care providers who now must take into account information channels available to their patients that are beyond their professional influence. The DTC availability of genome analyses already

today requires new approaches in genetic counselling – by the companies selling the test, as a service feature, and also by the regular health care providers to whom individuals will likely turn for follow-up interpretation and advice. Strategies in public health genomics must take these new realities into account.

8.3 Ethics: challenges from within

The challenges to ethics do not only come from the part of genomic science. As a dynamic, living discipline it also faces challenges from within the discipline itself, like the need for continuous theory development, and the need to reflect upon the boundaries of its competency when reacting to calls for expertise. Two examples of such challenges are outlined below: the challenge of dealing with moral diversity, and of determining the position of ethicists as insiders or outsiders in providing moral guidance.

8.3.1 *Global science and local ethics*

As noted in the overview article in Chapter 1, mainstream Western world biomedical ethics is taken as a reference throughout this study. This should not be interpreted as a lack of awareness of the existence of great traditions of ethics in many parts of the world. Rather, it is chosen here as a starting point because of its role in framing regulation and guidelines for research worldwide: the dominant governance model is a thoroughly Western one. Western culture, values and resources are also predominant in the design (and therefore in the criteria for funding) and in the conduct of human genetics research, regardless of the place where these studies actually take place or of the cultural background of the research subjects. Even if efforts are being made to adjust to this diversity, these efforts in themselves may actually accentuate the incommensurability of values and, at the practical level show the clash of interests between the researchers and the participating communities. For example, in the International HapMap project, a conflict emerged between Nigerian research oversight and the HapMap's funding agencies (notably the NIH) about appropriate financial compensation for the Yoruba community involved. The Yoruba already had received some extra funds for the enhancement of local primary health care services. Later, additional funds were requested as a demonstration of reciprocity for the community's involvement. This raised difficult issues, also concerning equal treatment of other participating communities. It was found that established international guidelines on human subjects research could not adequately 'solve' the problem. The Chinese and Japanese communities raised different issues, they were concerned in particular about the extent of the use of the donated samples that they fear to be in future beyond their control.[11]
A critical analysis of case studies in the governance of global genomics has been conducted recently in the interdisciplinary Genes without Borders project.[12] From the viewpoint of ethics the problem becomes particularly clear when scrutinizing the applicability of a principle-based approach to the design of various kinds of research guidelines. Providing *pragmatic moral guidance* might require different principles in different parts of the world. That does not

necessarily mean a turn towards crude moral relativism, but can be interpreted as the recognition of the existence of moral pluralism within particular moralities.[13] It is a matter of fact that value systems differ, resulting in incommensurability of the meaning (as content) of principles because the underlying concepts differ. This may even hold true for virtues. Apparently shared notions can represent very different concepts. The notion of 'altruism', for example, has recently been highlighted as 'health-information altruism' by Kohane and Altman.[14] In Chapter 2, *Shifting trends in ethics*, it is referred to as deserving serious consideration in post-genomics research ethics and is therefore highly relevant in the current context. But, what do we mean by altruism and where are the limits of this virtue? As mentioned above in the example of community contribution to the HapMap project, the interpretation of altruism and the appropriateness of substantial financial compensation for altruistic research participation may differ considerably between cultures.
Even more profound: what is the precise content of altruism? To give just one example, the notion of 'altruism' also refers to a key concept in Buddhism, that may or may not be commensurable with non-Buddhist concepts, the meaning of the constituent notions being rooted in a highly particularistic moral framework, as the following will show. The basic content of Buddhist 'altruism' would consist of two layers: (a) the attitude and action of non-injury (*ahiṃsā*), that is, refraining from inflicting harm or injury to other sentient beings (including human beings). This may be described as "passive altruism". And in addition to that, (b) the attitude and action of actively benefiting other beings, which may be described as "active altruism" (one of the motives for the action being 'compassion': *karuṇā*).[15] Another feature Buddhist philosophy that specifically leads to – seemingly – incommensurability with Western world biomedical ethics is the denial of the existence of a permanent Self.[16,17] Obviously, this impacts on crucial Western concepts like autonomy. The reading of the traditional canonical meaning and the scope of later interpretations, as well as dealing with the question of whether a concept of 'autonomy' can be found in Buddhism, is subject to disputes beyond the scope of the current context.[18,19]
Another well-known example of basic incommensurability is the status of the individual versus the family in matters of disclosure and decision-making in the Confucian moral tradition that prevails in large parts of China. Its concept of moral agency differs profoundly from the concepts that Western world biomedical ethics' reasoning about autonomy, consent, and paternalism (to only mention a few relevant topics) is built upon.[20] The issue of a relevant conceptual misunderstanding as demonstrated in these examples is not far-fetched if one is aware of the predominance of respectively Buddhist and Confucian normative frameworks in a number of Asian countries that are increasingly powerful players in the genomic sciences. They can be approached in an anthropological/ethnographic way, but they are genuine matters of philosophy and ethics in the first place. Obviously, they are also at the heart of any debate about consensus.[21]

Besides, there is the other context of explanation, notably in theoretical biology[22] and economy[23], that describes the concepts of altruism and reciprocity in biological terms and in

particular as outcomes of gene-culture co-evolution. Some of the assumptions being increasingly empirically corroborated not only by game-theoretical experiments but also by the neurosciences, in particular through neuroimaging.[24] This is the further challenge already around the corner: mastering the understanding and integration of these different explanatory models. Systems-based approaches will be the only way to reach these aims.[25]

8.3.2 *Ethics: by insiders or outsiders?*

A further issue I want to raise here – relevant to the perspective from which the case studies in this thesis have been presented – is concerned with the position of professional ethicists in an interdisciplinary context. Are they a member of the club or are they floating above?
Philosophers – and ethicists – can be insiders or outsiders, as Frances Kamm noted in 1990, referring to involvement with commissions. She concludes: "The insider philosopher who serves a commission should think of his primary duties as informing and philosophizing with the commissioners, rather than producing a perfect philosophical document or acting directly for the public good. The insider philosopher's duty may[26] include considering the meta-question of moralized compromise procedures".[27] As insiders they give direct advice, as outsiders they comment upon this activity and its outcomes which is the case when philosophers and ethicists comment upon the work and reports of commissions. One can be an insider on one occasion and an outsider on another. Earlier, in 1987, Dan Brock had analyzed the role of philosophers in policymaking and argued for a different professional responsibility of philosophers when working on academic questions from when providing expertise in the public realm.[28] As long as there is philosophy, there has been reflection upon philosophers' roles. Today, the discipline of ethics is in the spotlights and with that the light is on the professional ethicists, and it is their professional involvement that I am referring to here.
Already at the time that early ELSI activities were initiated there was a considerable awareness within the profession about the issues related to the professional role of philosophers/ethicists when acting as advisors on moral matters, e.g. when called upon for providing pragmatic moral guidance in commissions or interdisciplinary working parties. It is this type of activities that Kamm and Brock (among a number of other authors) refer to.
It is evident that this involvement has only increased with the growth and the pervasiveness of genomics. However, attention must be paid to the fact that many activities are called "bioethics" that are neither philosophical nor related to professional ethics, and the players involved coming from all disciplines except for ethics and philosophy. It is e.g. quite common that "ethics committees" do not include any professional ethicist at all. This may occur in any type of ethics commission, it has been investigated recently by Salter and Jones with regard to commissions at biobanks.[29]
Moreover, apart from the work in commissions and working groups there is a further context of involvement of philosophers, broadly as philosophers or in the narrower sense as ethicists or bioethicists. The workplace is at the lab bench and the partners in the dialogue are the scientists who are in practice working on the matters under discussion. At the benchside there are two

types of philosophical insiders. In the concept of "benchside ethics consultation" the ethicists are insiders – as they face ethical dilemma's directly and give advice – but they come as outsiders to the lab.[30] The other insider role is as a member of the team. It is from that particular perspective that the case studies in this thesis have been presented.
The case study in Chapter 4 deals with the model of 'open consent' in the Personal Genome Project that has been developed and – having passed the approval procedures of the Harvard Medical School IRB – put into practice by a small multidisciplinary team that included a professional ethicist as a team member.[31] Undeniably, this implies a bias on the part of the ethicist. However, this does not automatically pose a threat to the ethicist's professional integrity, as also within the context of a team the philosopher's core job remains seeking clarification of arguments (a Socratic activity indeed, as Ashcroft notes)[32] and striving for the achievement of rational decisions, rather than reasonable consensus. The philosopher's argument may not win in the end, but keeping up professional standards implies accepting dissent and a minority position.
The role of the ethicist has been similar in the case study presented in Chapter 5, the analysis of the requirements for appropriate consent language for the PGRN Data Sharing Action Group. The research was carried out by me, as a professional ethicist being an Affiliate Member of the PGRN and involved with the Data Sharing Working Group.

8.4 Final remarks

Having arrived at the end of this study – what are the conclusions, and what are the hypotheses resulting from the investigation? Can any pragmatic moral guidance be offered?

I set out to investigate the shaping of biomedical ethics, as a particular branch of applied ethics, by the development of the genomic sciences over the past three decades. It was found that the development of a rights-based ethics and the growing emphasis on procedural aspects coincided with a call for procedural ethics' guidance. This occurred initially at the scale of national policy making (in the United States, but also in The Netherlands), and later at the regional level (the European Union), followed by the supranational development of governance structures within the scientific community of the genomic sciences, as, for example, through the Human Genome Organization.
For a long time, this rights-based procedural type of ethics was well suited for meeting the demands brought on by its institutionalization.
Traditional 'tasks' for ethics and ethicist, as for example designing informed consent for study participation could be performed within the governance frameworks that had been created – thereby, reinforcing the image of ethics as an instrument of governance.
Now, this particular use of ethics is no longer adequate and stretches the discipline to its limits. The extreme pace of technology development along with the establishment of new conceptual approaches – in particular, the increasing application of systems biology and the developments

in bioinformatics – together with the expansion of the group of relevant global players in the genomic sciences call for novel steps also within ethics.

The way to proceed may be bottom-up, with innovation starting at the level of practical applications like consent protocols and the establishment of new forms of agency of study participants, as has been put into practice in the Personal Genome Project. These concrete developments may spark changes in the role that ethics plays at the level of research design and governance.
New conceptual demands to ethics stem from theory development in the sciences, as well as from the involvement of parties representing normative frameworks that differ substantially from mainstream Western-world biomedical ethics. Addressing these challenges will call for critical philosophical inquiry with possibly inconvenient outcomes. Increased effectiveness of ethics may result in less smooth consensus.

Pragmatic moral guidance starts with the caveat that we can reach provisional conclusions at most, raising further questions along with a growth of knowledge that cannot be tamed. It is an open-ended process and in the case of the genomic sciences it develops incredibly fast. We must be audacious and *prometheus*, well aware that the facts will always be ahead of us.

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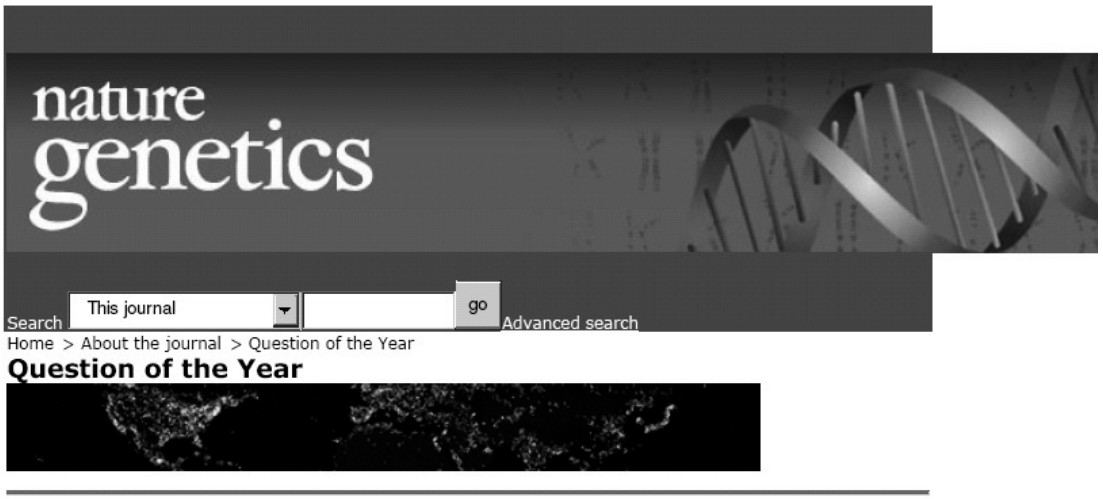
9.

Epilogue
The $1000 Genome

Jeantine Lunshof . A just distribution of benefits. Reply to Question of the Year.
Nature Genetics, 2 April 2007

http://www.nature.com/ng/qoty/index.html



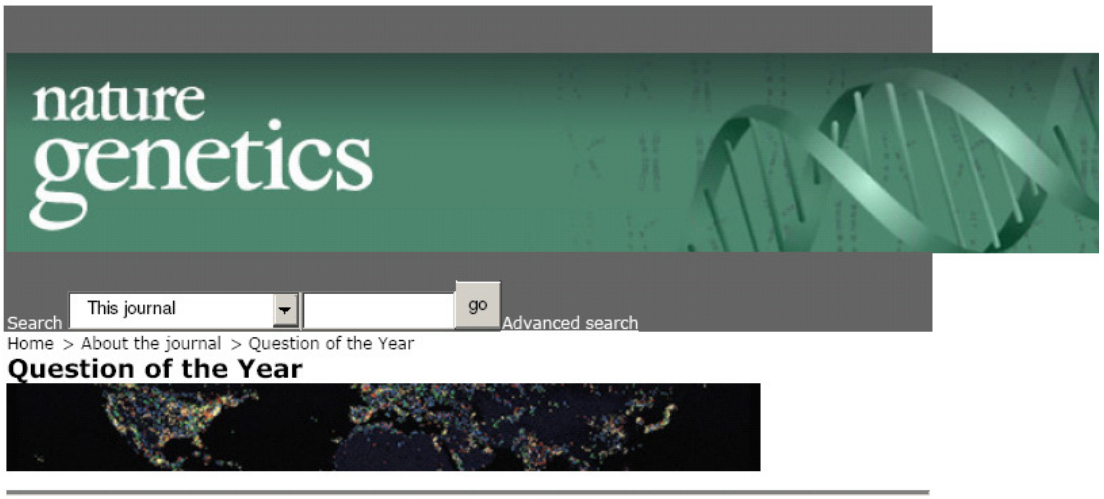
The sequencing of the equivalent of an entire human genome for $1,000 has been announced as a goal for the genetics community, and new technologies suggest that reaching this goal is a matter of when, rather than if. What then? In celebration of its upcoming 15th anniversary, Nature Genetics is asking prominent geneticists to weigh in on this question: what would you do if this sequencing capacity were available immediately? This new Nature Genetics 'Question of the Year' website, sponsored by Applied Biosystems, will reveal their answers. The website will be updated monthly, so check back regularly to get a glimpse of the future of genetics.

Sponsor: Applied Biosystems

- John Quackenbush (Dana-Farber Cancer Institute)
- Walter Bodmer (Oxford University)
- Jun Yu (Beijing Institute of Genomics)
- Tayfun Ozcelik (Bilkent University, Turkey)
- Samir K. Brahmachari (Institute of Genomics & Integrative Biology, New Delhi)
- Michael Stratton (Wellcome Trust Sanger Institute)
- James R. Lupski (Baylor College of Medicine)
- Peter Little (University of New South Wales, Sydney)
- Rasmus Nielsen (University of Copenhagen)
- Michal Pravenec (Institute of Physiology, Czech Academy of Sciences)
- Elizabeth M.C. Fisher (University College London)
- Takashi Gojobori (National Institute of Genetics, Japan)
- Richard Cotton (Genomic Disorders Research Centre)
- Emmanouil T. Dermitzakis (Wellcome Trust Sanger Institute)
- Hong-Xuan Lin (Shanghai Institute of Plant Physiology and Ecology)
- Michael D. Rhodes (Applied Biosystems)
- Bruce Lahn (University of Chicago)
- Leena Peltonen-Palotie (University of Helsinki)
- Paul Nurse (Rockefeller University)
- Manel Esteller (Spanish National Cancer Centre)
- Julian Parkhill (Wellcome Trust Sanger Institute)
- Sergio Verjovski-Almeida (University of São Paulo)
- Yoshihide Hayashizaki (RIKEN Yokohama Institute)
- Joseph Nadeau (Case Western Reserve University)
- Muntaser E. Ibrahim (University of Khartoum)
- Jeantine Lunshof (Vrije University Medical Center)
- Sarah Tishkoff (University of Maryland)
- Stephen Scherer (Hospital for Sick Children/University of Toronto)
- Laurence D. Hurst (University of Bath)
- John Ioannidis (University of Ioannina and Tufts University)
- Emma Whitelaw (Queensland Institute of Medical Research)
- Elaine A. Ostrander (National Human Genome Research Institute)
- Christine Petit (Pasteur Institute)
- Axel Meyer (University of Konstanz)
- David Goldstein (Duke University)
- David Gurwitz (Tel Aviv University)
- Detlef Weigel (Max Planck Institute for Developmental Biology)
- Ewan Birney (European Bioinformatics Institute)
- Leonid Kruglyak (Princeton University)
- Les Biesecker (National Human Genome Research Institute)
- Eric Green (National Human Genome Research Institute)
- Richard Gibbs (Baylor College of Medicine)
- Trudy Mackay (North Carolina State University)
- Thomas Mitchell-Olds (Duke University)
- Francis S. Collins (National Human Genome Research Institute)
- George Church (Harvard Medical School)
- Stephen J. O'Brien (National Cancer Institute)
- Evan Eichler (University of Washington)
- Jonathan Pritchard (University of Chicago)

… and others in the course of the year

http://www.nature.com/ng/qoty/index.html



NG: What would you do if it became possible to sequence the equivalent of a full human genome for only $1,000?

Jeantine Lunshof (Vrije University Medical Center): a just distribution of benefits

Being a philosopher, I will go for a walk in the park when the $1,000 genome arrives, and make up my mind. By now we should have learned to be prometheus—forward-thinking, audaciously, while at the same time accepting that the humanities cannot run ahead of science. Therefore, we should take any conceivable scenario and application into consideration and hope for incremental implementation that will allow us to keep pace. Quite a few ethical problems might be solved, or at least reduced, by the general availability of individual genomes or, for now, exomes. The complex questions raised by stratification and its related group-based stigmatization may become obsolete once health risk estimates can be based on a comprehensive analysis of individual genomes. The use of comprehensive data sets in research using genome-wide association studies already confronts institutional review boards with qualitatively new questions that cannot be answered by applying the traditional criteria for ethical acceptability. At the same time, new questions will arise, such as how to assure health care equity with increasing individualization and limited resources. In clinical practice, the availability of this new type of information should improve the efficiency of therapy as well as prevention; however, a huge translational and educational effort will be needed to make it work. In biomedical research, a refinement of studies based on new modes of stratification may increase the number of studies needed and require many more research subjects. The resulting new products, including drug-test combinations, might be safer and more efficacious but have smaller markets. Such products might then be so expensive that few will benefit. From the point of view of ethics, the big challenge of the $1,000 genome will be in dealing with its mixed blessings. The humanities should join science now in a cooperative effort to reduce the adverse effects and optimize the benefits, securing their just distribution.

(posted 2 April 2007)

10.

Summary
Samenvatting

10.1 Summary

The new genomics: challenges for ethics

Are new concepts needed in biomedical ethics to keep pace with the developments in post-Human Genome Project genomics?
This thesis examines the challenges that developments in post-Human Genome Project (HGP) genomics pose to the established concepts and practices of – Western world – biomedical ethics. These challenges are relevant to the various roles that ethics plays, as for example, its role in the design and the conduct of research, its role in the translation of knowledge and technologies beyond the research stage, and its role as an instrument of governance.
In short, the question here is not about the ways in which ethics influences genomics, as for example by putting constraints on certain applications, but rather the other way round: how does genomics impact on applied ethics and on the role of ethicists. And: what does it mean for the future, given the pace of the developments in the genomics sciences.

Chapter 1

Chapter 1 provides a broad **Introduction** into the background of the underlying questions and examines how ethics could become a governance tool. It is shown how developments in genetics and genomics coincided with the emergence of a rights-based approach in biomedical ethics, putting emphasis on procedural aspects and on the role that ethics could – or, as assumed for many years: should – play in policy making. This role was reinforced through the institutionalization of ethics in genomics in the form of ELSI and ELSA programs and the establishment of ethics within the Human Genome Organization already in its early years. Chapter 1 also describes the aim of the study, as "to analyze the role of ethics in genomics and the related sciences and to generate hypotheses concerning future developments in ethics, taking into account the likely paradigm shift in the genomic sciences towards systems biology". Concerning the method, reasons are given for taking a hypothesis-generating approach that appears as most appropriate given the dynamics of the developments in genomics. Chapter 1 also includes a short glossary and an overview of the further chapters.

Chapter 2

The new genomics: new challenges for ethics? The article *The new genomics and personal genome information: ethical issues* takes the 'new style' personal genome information as an example to explore the questions that are raised by developments in next-generation sequencing technologies. Starting point is the consideration that "… ethical thinking will inevitably continue to evolve as the science does …" . This supports the claim that current biomedical ethics is no longer fully adequate for addressing the normative issues that arise in the context of post-Human Genome Project Genomics. The advances in sequencing technology are one

example of the very fast developments in genomics where increasing pace and scale require new concepts in large-scale research ethics. Traditional issues of confidentiality and consent are in need of critical review. The global impact of genomics sciences accentuates this need.

Chapter 3

The chapter **Shifting trends in ethics** discusses in the article *Personalized medicine: new perspectives – new ethics?* the applicability of protection-paradigm based principles to questions arising from the potential conflict between individual and collective interests in population-based genomic research. The development of personalized medicine and, in particular, pharmacogenomics, is taken as an example to demonstrate the need for a new normative framework that comprises new principles like reciprocity, mutuality, solidarity and citizenry, as has been proposed recently. In this context, the concepts of equity and altruism – in particular in the form of health-information altruism deserve scrutiny. Postgenomic medical and research ethics is put in the perspective of a development from traditional medical ethics, clinical research ethics to large scale (genomics) research ethics. It is argued that there is an urgent need for professional ethicists to pro-actively address the new challenges.

Chapter 4

The chapter **Genomics for all: ethical implications for clinical practice** presents some possible consequences for the physician-patient interaction in view of the new reality of comprehensive personal genome information being available to any individual who wishes to purchase it: *Hippocrates revisited? Old ideals and new realities.* On the other hand, personal information is also being made available to the broad scientific community and to some extent to the public in the new types of studies with open-access databases. This implies giving up (much of) confidentiality and privacy. Once again, this impacts upon consent and requires careful reflection on and renewal of mutual trust in the patient-physician relationship.

Chapter 5

New roads to consent. In search of pragmatic moral guidance. This chapter zooms in on the first demonstration case of this study: The Personal Genome Project. It addresses the concrete question of obtaining valid consent for participation in state-of-the-art genomics research that involves collecting and sharing of comprehensive genotype-phenotype data sets. In *From genetic privacy to open consent* it is argued that 'veracity' should be the primary moral principle guiding novel models of consent. It is argued that taking seriously threats to privacy and confidentiality, in particular in many situations in daily life, leads to the conclusion that promises of privacy and confidentiality cannot realistically be made to participants in biomedical research and, therefore, should not be conditions for consent. Telling the truth about the accessibility of research data will imply asking participants to consent to this degree of

openness. Individuals who are not comfortable with this idea should likely refrain from participation in research. Alternative solutions are scarce.

Chapter 6

The second case study is presented in Chapter 6, **Current challenges for consent: pharmacogenomics, data sharing, and the language of consent** that consist of two papers showing in which ways current biomedical ethics has reached its limits, taking developments in pharmacogenomics as a model case. In the first paper *A Call for the Creation of Personalized Medicine Databases* we argue for data sharing that includes the vast extant data bases of industry. A moral obligation may exist to use all data that individuals made available for purposes of health research. The ethical challenges arising in the context of data sharing relate to reciprocity, universality and solidarity, and this concerns, among other things, ownership of genomic information, public trust and the requirement of transparency. It remains to be seen, whether the sharing of data between industry and academia can be effectuated by an appeal to 'moral' obligations or that binding regulation (using ethics as instrument for its justification?) will be inevitable.

The second paper in this chapter consists of a working draft of a white paper for the NIH/NIGMS prepared on behalf of the Pharmacogenetics Research Network Data Sharing Action Group: *Pharmacogenetics, data sharing, and biobanking: the scope and limits of consent.*
Designing consent for prospective data collection is less 'difficult' than finding an appropriate way of dealing with extant data (and samples) that are stored in databases and repositories and have been collected long ago – often for other purposes and with widely varying terms of consent. Today, research uses the data from yesterday. But, today we are also generating the extant data of tomorrow. For example in pharmacogenomics research the building of very large well-curated databases and the use of all relevant extant data is indispensable for generating reliable, validated knowledge that will be clinically applicable. A large network like the Pharmacogenetics Research Network has a particular interest in and societal responsibility for making available appropriately consented data.

Chapter 7

Chapter 7 contains an **Outlook on theory development and education**. The article *Teaching and practicing pharmacogenomics: a complex matter* discusses the importance of the application of systems biology approaches to pharmacogenomics. In particular, attention is paid to the implications of this paradigm shift for the current and future curricula in the biomedical sciences that shall enable implementation of the new approach in clinical practice.

Chapter 8

Chapter 8 contains the **General Discussion**. This chapter recapitulates the initial questions concerning the role of ethics in genomics and, in particular, the impact upon ethics of the developments in the genomic sciences. The challenges, as posed by these developments are addressed, notably concerning scale and pace, technology and methods, theory development in the sciences up to an evolving paradigm shift, and novel practices. Ethics also faces challenges from 'within': the global science of genomics meets local ethics. Examples of 'particular moralities' – Cofucianism and Buddhism respectively – are presented. Finally, the role is addressed of professional ethicists as involved with science, as 'insiders' or 'outsiders'.

Epilogue

An **epilogue** on **The $1000 genome** entails a reply to Nature Genetics' Question of the Year in 2007, and discusses the moral desirability of *A just distribution of benefits*.

10.2 Samenvatting

New genomics: ethiek op de proef gesteld

Zijn er in de biomedische ethiek nieuwe concepten nodig om de ontwikkelingen in het post-Human Genome Project (HGP) tijdperk te kunnen bijbenen?
Dit proefschrift onderzoekt op welke wijze de ontwikkelingen in post-HGP genomics de gevestigde praktijk en concepten van – Westerse – biomedische ethiek op de proef stellen. Dit is vooral relevant omdat ethiek diverse belangrijke rollen vervult, bijvoorbeeld in de opzet en uitvoering van onderzoek, in de omzetting van kennis en technologieën naar de praktijk en ook in het bijzonder als beleidsinstrument.
Kortom, het gaat hier niet om de vraag op welke wijze genomics door ethiek beïnvloed wordt, zoals bijvoorbeeld door beperkingen te (willen) stellen aan bepaalde toepassingen, maar het is hier andersom: op welke wijze beïnvloedt genomics de praktische ethiek en de rol van ethici. Een verdere vraag is wat dit voor de toekomst betekent, gezien de enorme snelheid waarmee de aan genomics gerelateerde wetenschappen zich ontwikkelen.

Hoofdstuk 1

De **Inleiding** – Hoofdstuk 1 – geeft een brede beschrijving van de vragen die het uitgangspunt voor het verdere onderzoek vormen en het gaat in op de vraag hoe ethiek tot een beleidsinstrument kon worden. Het hoofdstuk laat zien hoe ontwikkelingen in de genetica en later in genomics toevallig samenvielen met de opkomst van een richting in de ethiek die sterk op (morele) rechten georiënteerd is. Daardoor werd het procedurele gebruik van ethiek sterk benadrukt en dit maakte het plausibel dat ethiek een belangrijke rol zou kunnen – of zou moeten – spelen in beleid: ethiek als instrument van ‘governance’. Deze procedurele functie van ethiek werd nog verder versterkt doordat er een ‘institutionalisering’ van ethiek in de context van genomics plaatsvond, in de vorm van de speciale ELSI en ELSA (ethische, juridische en sociale aspecten) programma’s binnen de kaders van het onderzoek in de genetica/genomics. De Human Genome Organization (HUGO) installeerde al vroeg een werkgroep ethiek binnen de organisatie.
Het doel van de studie wordt in dit eerste hoofdstuk omschreven als:

> “een analyse van de rol van ethiek in genomics en de verwante wetenschappen en het genereren van hypotheses ten aanzien van toekomstige ontwikkelingen op ethisch gebied, met name gezien de zich voltrekkende paradigmawisseling in genomics en daaraan gerelateerde wetenschappen in de richting van systeem biologie”.

De hypothese-genererende benadering van deze studie past bij de dynamiek van de ontwikkelingen in genomics.
Het eerste hoofdstuk bevat ook een korte beschrijving van een aantal kernbegrippen en een overzicht van de verdere hoofdstukken.

Hoofdstuk 2

The new genomics: new challenges for ethics? (*New genomics*: een nieuwe uitdaging voor de ethiek?). Het artikel *The new genomics and personal genome information: ethical issues* onderzoekt aan de hand van het voorbeeld van informatie over het individuele genoom wat voor soort vragen de ontwikkeling in de sequentieer-technologie (next-generation sequencing technologies) met zich mee kan brengen.
Uitgangspunt is de overweging dat "… het denken in de ethiek zich noodzakelijk verder zal ontwikkelen parallel aan de ontwikkeling van de wetenschap …" (origineel: "… ethical thinking will inevitably continue to evolve as the science does …").
Dit onderbouwt de veronderstelling dat de huidige biomedische ethiek niet langer volledig toereikend is voor de behandeling van de normatieve kwesties die zich voordoen in de context van de nieuwe (post-HGP) genomics. De vooruitgang in de sequentieer-technologie is slechts een voorbeeld van de uiterst snelle ontwikkelingen in de genomics wetenschappen – deze versnelling en tegelijkertijd schaalvergroting vereisen nieuwe concepten ook in de ethiek, toegesneden op zeer grootschalig onderzoek.
Traditionele kwesties in de ethiek zoals geheimhouding en toestemming komen onder druk te staan en moeten opnieuw bekeken worden. Het globale karakter van genomics en verwante wetenschappen en toepassingen maakt een herbezinning nog dringender.

Hoofdstuk 3

In het derde hoofdstuk, **Shifting trends in ethics** (Trendverschuiving in de ethiek), stelt het artikel *Personalized medicine: new perspectives – new ethics?* aan de orde of de gangbare, op het 'protectie-paradigma' gebaseerde ethische principes toepasbaar zijn op vragen die voortkomen uit het conflict tussen individuele en collectieve belangen dat zich kan voordoen bij genomics onderzoek in populaties. Aan de hand van de ontwikkeling van 'personalized medicine' , en in het bijzonder pharmacogenomics, wordt de behoefte aan een nieuw normatief kader verduidelijkt, een kader dat principes als 'reciprocity' (wederkerigheid), 'mutuality' (gemeenschappelijkheid), 'solidarity' en 'citizenry' omvat, zoals recent voorgesteld werd. In dit kader verdienen ook concepten als 'equity' en altruïsme de aandacht – wat betreft het laatste vooral het concept van 'gezondheidsgegevens-altruisme'. De zogenaamde 'postgenomische' medische en research ethiek wordt in het perspectief geplaatst van een ontwikkeling van traditionele medische ethiek, via ethiek van klinisch onderzoek naar een ethiek die is toegesneden op grootschalig (genomics) onderzoek. Het hoofdstuk roept de professionele ethici op zich proactief met deze kwesties bezig te houden.

Hoofdstuk 4

In **Genomics for all: ethical implications for clinical practice** (Genomics voor iedereen: ethische implicaties voor de klinische praktijk) worden enkele van de mogelijke gevolgen voor de arts-patiënt relatie aan de orde gesteld van het beschikbaar komen van omvattende informatie

over het eigen genoom zoals die vandaag de dag commercieel verkrijgbaar is. Anderzijds is individuele informatie ook in toenemende mate beschikbaar voor brede groepen van onderzoekers en tot op zekere hoogte ook voor het publiek in het kader van de nieuwe onderzoeksmodellen waarbij breed toegankelijke databanken ingericht worden. Dit betekent dat een substantieel stuk geheimhouding en privacy prijsgegeven wordt. Het hoofdstuk bevat het artikel *Hippocrates revisited? Old ideals and new realities.*

Hoofdstuk 5

New roads to consent. In search of pragmatic moral guidance (Nieuwe wegen voor toestemming. Op zoek naar pragmatische morele aanwijzingen). In dit hoofdstuk komt de eerste concrete casus van dit onderzoek aan de orde: het Personal Genome Project. Het artikel *From genetic privacy to open consent* gaat in op de concrete vraag of werkelijk geldig informed consent kan worden verkregen voor geavanceerd genomics onderzoek dat het verzamelen en delen van omvattende genotype/fenotype gegevens inhoudt. Het artikel betoogt, dat 'veracity' (waarachtigheid; oprechtheid) het allereerste en leidende morele principe moet zijn bij de ontwikkeling van nieuwe modellen voor consent. Wanneer wij de ondermijning en uitholling van privacy en geheimhouding zoals die in vele situaties voorkomt serieus nemen, dan moeten wij concluderen dat ook in het kader van biomedisch onderzoek beloftes van privacy en geheimhouding niet waargemaakt kunnen worden en daarom dus zeker geen voorwaarde voor het verkrijgen van consent moeten zijn. Indien men onderzoeksdeelnemers naar waarheid informeert over de mate van toegankelijkheid van onderzoeksgegevens, dan zal men hun moeten vragen daarmee uitdrukkelijk in te stemmen. Mensen voor wie dit niet acceptabel is zullen van deelname aan wetenschappelijk onderzoek af moeten zien. Er zijn weinig alternatieven.

Hoofdstuk 6

De tweede casus wordt gepresenteerd in hoofdstuk 6, **Current challenges for consent: pharmacogenomics, data sharing, and the language of consent** (Actuele uitdagingen voor toestemming: pharmacogenomics, delen van data en de taal van toestemming). Dit hoofdstuk bevat twee teksten die aan de hand van ontwikkelingen in pharmacogenomics laten zien waar de huidige biomedische ethiek op haar grenzen stuit. Het eerste artikel *A Call for the Creation of Personalized Medicine Databases* behelst een pleidooi voor het delen van data en het uitwisselen van informatie met inbegrip van de omvangrijke bestaande databestanden bij de industrie. Een morele verplichting kan aangenomen worden voor het optimale gebruik van alle gegevens die individuen beschikbaar hebben gesteld voor gezondheid gerelateerd onderzoek. De ethische knelpunten die zich voordoen in de context van het delen van data hebben betrekking op 'reciprocity', 'universality' en solidariteit en het gaat daarbij om, onder andere, eigendom van genetische informatie, het openbare vertrouwen en de eis van transparantie. Het valt nog te bezien of uitwisseling van data tussen de industrie en de academische wereld

bewerkstelligd kan worden door een beroep te doen op ‘morele’ verplichtingen of dat bindende regelgeving (waarbij de ethiek gebruikt wordt als middel ter rechtvaardiging?) onontkoombaar zal zijn.

De tweede tekst in dit hoofdstuk bestaat uit een voorlopig werkdocument dat door de Data Sharing Action group van het Pharmacogenetics Research Network voorbereid werd ten behoeve van discussie binnen de National Institutes of Health/National Institute of General Medical Sciences (USA): *Pharmacogenetics, data sharing, and biobanking: the scope and limits of consent*. Het ontwerpen van toestemming voor toekomstige data verzameling is veel minder ‘moeilijk’ dan het vinden van een passende manier om met bestaande gegevens (en monsters) om te gaan. Dit in biobanken opgeslagen materiaal is vaak lang geleden verzameld, veelal voor geheel andere doelen en er is een enorme variëteit aan formuleringen van de toestemming voor gebruik. Vandaag gebruiken wij de gegevens van gisteren. Maar, wij genereren ook vandaag de ‘oude’ data van morgen. In het pharmacogenomics onderzoek, bijvoorbeeld, is het opbouwen van zeer grote en goed beheerde en ontsloten databestanden die het gebruik van alle relevante bestaande data mogelijk maken, een noodzakelijke voorwaarde voor het genereren van betrouwbare, valide kennis die uiteindelijk klinisch toepasbaar zal zijn. Een groot netwerk als het Pharmacogenetics Research Network heeft een bijzonder belang – en een grote maatschappelijke verantwoordelijkheid – bij het beschikbaar maken van gegevens waarvoor passende toestemming gegeven is.

Hoofdstuk 7

Hoofdstuk 7, **Outlook on theory development and education**, behandelt aspecten van theorieontwikkeling en onderwijs. Het artikel *Teaching and practicing pharmacogenomics: a complex matter* gaat in op de toepassing van systeembiologie en het belang daarvan voor pharmacogenomics. Het artikel besteedt in het bijzonder aandacht aan de gevolgen die deze paradigmawisseling heeft voor de huidige en de toekomstige curricula in de biomedische wetenschappen – via deze wetenschappen zal de nieuwe benadering uiteindelijk ingang kunnen vinden in de klinische praktijk.

Hoofdstuk 8

Hoofdstuk 8 is gewijd aan de Discussie. Dit hoofdstuk grijpt terug naar de oorspronkelijke vraagstelling over de rol van ethiek in genomics en in het bijzonder de vraag naar de uitwerking die de ontwikkelingen in genomics en verwante wetenschappen op de ethiek hebben. Het hoofdstuk gaat in op de diverse aspecten van deze uitdaging, met name de grootschaligheid en de snelheid, de technologie en de methoden, de theorieontwikkeling in de biologische wetenschappen uitlopend op een paradigmawisseling, daarnaast zijn er ook innovatieve praktijken.

De ethiek is ook geconfronteerd met een uitdaging van ‘binnen uit’: een globale genomics wetenschap stuit op lokale ethieken. Enkele voorbeelden van zulke ‘particular moralities’ – namelijk het confucianisme en het boedddhisme – worden kort voorgesteld. Tenslotte komt ook de rol van de professionele ethici aan de orde en hun betrokkenheid bij (natuur)wetenschappen. Ethici kunnen daarin een ‘insider’ of een ‘outsider’ rol vervullen.

Epiloog

Uiteindelijk is er een nawoord. Het statement over **The $1000 genome** is een antwoord op de *“Question of the Year”* die Nature Genetics in 2007 stelde. Het antwoord gaat in op de morele wenselijkheid van een rechtvaardige verdeling van de baten en voordelen van de ontwikkeling in met name de sequentieer-technologie en pleit voor *A just distribution of benefits.*

11.

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Late, but not too late, I arrived at the Department of Molecular Cell Physiology of VU University. So far, I could only set the first steps on the new research path into the philosophy of systems biology.
Hans Westerhoff: thank you so very much for welcoming as a guest the stranger that knocked on your door. Being able to stay at your department, meant a great encouragement and it also substantially aided me in finalizing the work on this thesis.
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Doing research while moving around – physically and virtually – between institutions would not be possible without the logistic support (and practical wisdom) of administrative and management staff. I want to thank Marianne Hardonk, Joy Bakker and Michel Telkamp at VUmc, Jeannet Wijker at VU University Amsterdam, Mayra Mollinedo and Yveta Masarova in Boston, and Mel Evans in Cardiff.

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12.

Professional biography

Professional biography

After receiving my Bachelor in Philosophy, and, as a minor, Tibetan Language & Cultural Studies (Hamburg University, Germany), I graduated from the University of Amsterdam (UvA) with an MA in Philosophy (Systemic Philosophy, Ethics, Medical Ethics) and Health Law. Holding a RN as well, I was involved in clinical research at the clinic of the Netherlands Cancer Institute in Amsterdam, NL, from 1981 until 1989. From 1993 to 1996 I carried out research on normative issues in the context of human genetics at the Institute for Human Genetics of Heidelberg University, Germany. In Germany and in the Netherlands I gave lectures and seminars on ethical issues in clinical genetics and genetic counseling, as well as on end-of-life decision-making and legislation, and both topics were also subjects of earlier publications (see publication list). Since 1992, I have been involved in international research collaborations on ethical issues in human genetics.

The focus of my current work as a philosopher and bioethicist is on research in the field of human genetics and genomics, in particular on ethical and public policy aspects of Pharmacogenomics, Genome-Wide Association Studies (GWAS), Personalized Medicine, and on the Philosophy of Systems Biology. Current research interests also include exploring the usefulness of philosophical discourse practices for dealing with genomics' benchside questions.

I was affiliated with the VU university medical center, Department of Clinical Genetics, Section Community Genetics, and the EMGO Institute from 2004 till 2008. Since March 2008, I am affiliated with the Department of Molecular Cell Physiology of the Faculty of Earth and Life Sciences at VU University Amsterdam, NL. In September 2008, I became Assistant Professor of Social Medicine, associated with the European Centre for Public Health Genomics, at the Faculty of Health, Medicine and Life Sciences at Maastricht University.

Since 2006 I am an ethics consultant to the Personal Genome Project at the Genetics Department of Harvard Medical School, and to the “Genes without Borders” Project at the University of Vienna, Austria. Since 2006, I have been an Affiliate Member of the National Institutes of Health Pharmacogenetics Research Network (PGRN) and, in 2007, I became a Member of the Public Population Project in Genomics (P^3G) Consortium. I serve on several Editorial Boards.

The work on this thesis was performed in the course of my affiliation with the VU university medical center, Department of Clinical Genetics, Section Community Genetics, and the EMGO Institute. My thesis research has been supervised by Professor Ruth Chadwick of Cardiff University, and an affiliation with CESAGEN (University of Lancaster & Cardiff University, UK) was granted in November 2007.

13.

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